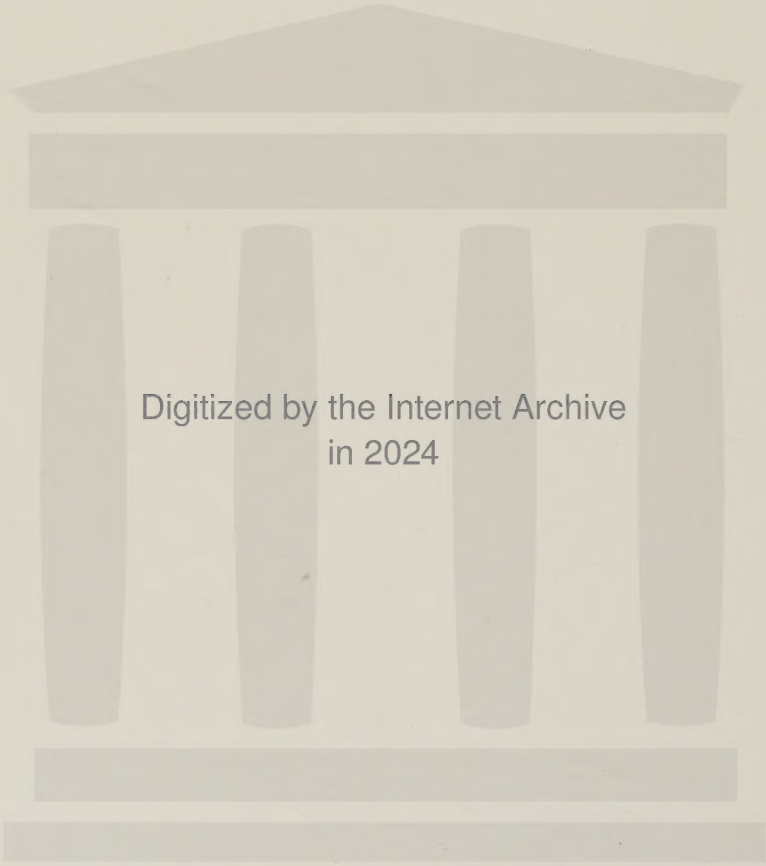
Robert Kreamer
2919 Cottage Grove
Des Moines, Iowa

My Dearest,
Use this book
as a guide to
help insure your
success as a
competent physician!
all my love,
Rhoda
6/1/56


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DISEASES OF THE HEART

By

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TO

MY WIFE

AND TO

R. M. F. AND B. J. F.

PREFACE

This book endeavors to provide a comprehensive and integrated exposition of the diseases of the heart. The swift pace of recent advances in this subject calls for a reorientation in presentation, and a modification in emphasis from that found in available standard works on cardiac disease.

In particular, special emphasis has been placed on the pathologic physiology of cardiac disorders, including the pathogenesis or mechanism of the symptoms and signs of circulatory failure, of angina pectoris and myocardial infarction, and of the various manifestations of the individual cardiac diseases. These discussions are not exhibited for mere academic consumption, but with the belief that an understanding of the dynamic events responsible for clinical phenomena is essential for maximum skill in diagnosis and treatment.

The increased utilization of quantitative measurements in the clinical study of circulatory disease is reflected in detailed discussions of the cardiac output, blood volume and extracellular volume, peripheral and intracardiac blood oxygen concentration and intracardiac pressures, body fluid and tissue electrolytes, and renal and pulmonary blood flow. Throughout the book these measurements are applied to clinical understanding and practical usage in the every-day diagnosis and treatment of cardiac disease.

Certain subjects of predominant importance have been presented as individual monographs. Ten chapters have been devoted to circulatory failure, eight chapters to diseases of the coronary circulation, and three to rheumatic fever and rheumatic heart disease. Bacterial endocarditis has been discussed extensively because it is the most frequent curable cardiac disease. Its bacteriological aspects have been presented in some detail because of their importance for effective diagnosis and treatment. Congenital heart disease has likewise been fully described because of the many recent advances in diagnosis and treatment. Special recognition has been given to cardiac catheterization, oxygen and pressure studies and angiocardiography as aids to the exact diagnosis essential for possible surgical treatment. The diagnosis and treatment of other remediable cardiac conditions have been emphasized, e.g., thyrocardiac disease, constrictive pericarditis, and heart failure due to anemia, avitaminosis, arteriovenous aneurysm and myxedema. Reference is also made to very recent advances in the surgical treatment of various clinical and experimental cardiac lesions including coronary artery disease, valvular disease and septal defects as well as other congenital anomalies, tumors and traumatic disturbances. To avoid repetition, no special chapter is devoted to cardiovascular emergencies, but appropriate discussions may be found rapidly by reference to the individual conditions under the heading "emergencies, acute cardiovascular" in the index.

Certain less common forms of cardiac disease have been described in greater detail than is usually found in standard books, e.g., cardiac disease related to endocrine, metabolic and nutritional disturbances, including also the cardiac effects of hemochromatosis, von Gierke's disease, xanthomatosis, amyloidosis and acute porphyria. Ample consideration has been given to the effects of various infections on the heart, to nonspecific myocarditis, and to other myocardial diseases of obscure origin, e.g., idiopathic hypertrophy, scleroderma and myotonia atrophica.

Roentgenology and electrocardiography have become essential elements of cardiologic practice and are thoroughly discussed throughout the book. Individual chapters devoted exclusively to a formal presentation of electrocardiography and roentgenology have been omitted, partly to avoid duplication and save space, but chiefly because as isolated subjects they could not be presented adequately in single chapters. Instead, emphasis has been placed on the application of electrocardiographic and roentgenologic interpretation to clinical practice, in which these findings must be integrated with the clinical history, symptomatology and other objective data.

Electrocardiography has been discussed in detail in connection with the arrhythmias, angina pectoris, myocardial infarction, pericarditis and myocardial disease, while both electrocardiography and roentgenology, including angiocardiography, have been amply considered in connection with such subjects as chamber enlargement, valvular heart disease and congenital cardiac lesions. To a lesser extent electrocardiographic and roentgenologic findings are also described in connection with almost every other type of heart disease, according to the importance and diagnostic value of these findings relative to other clinical features. A number of other graphic methods, including phonocardiography, roentgenkymography, electrokymography (fluorocardiography) and endocardial electrocardiography, have recently received increasing attention from cardiac investigators and these have been briefly mentioned when pertinent. However, because of their limited practical value at the present time these and other subjects in which the author may have a special interest have not been unjustly emphasized.

It is impossible to make specific acknowledgment to the host of individuals who, directly or indirectly, have helped provide the knowledge which is the basis for this book. I owe much to hospital colleagues and associates, and especially to Dr. Arthur Fishberg. Of the numerous teachers and collaborators to whom I am indebted I wish to mention specifically the late Dr. C. J. Rothberger of Vienna who trained me in experimental cardiology and electrocardiography, the late Dr. Louis Gross in cardiac pathology and the late Dr. Emanuel Libman in clinical cardiology.

For the opportunity of studying and utilizing the clinical material on his wards and for his encouragement in clinical research, I am especially grateful to Dr. George Baehr. I also wish to offer thanks to Dr. B. S. Oppenheimer and Dr. I. Snapper, under whom I have served for brief periods. Dr. A. Master kindly permitted my use of the electrocardiographic files and Dr. M. Sussman

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New York City CHARLES K. FRIEDBERG

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PART I

CIRCULATORY FAILURE

1

CARDIAC FUNCTION AND CARDIAC FAILURE

The function of the heart is to maintain an adequate output of blood at all times. Cardiac failure denotes that the output of the heart is insufficient for the needs of the tissues. Thus a normal cardiac output is not a fixed absolute value but must be assessed in terms of variable tissue requirements.

The failing heart may supply an adequate flow of blood when a patient is at rest but not under the stress of exercise, of pregnancy, of fever and infection or of hyperthyroidism. Under certain circumstances, e. g., severe anemia, the cardiac output of the patient at rest may even exceed that of normal individuals.[16, 2] Heart failure may be present despite this augmented cardiac output if the latter does not quite compensate for the deficiency in oxygen content of the blood, i. e., if the tissues do not receive their needed supply of oxygen despite an increased blood flow. The adequacy of cardiac function must therefore be defined not only in terms of cardiac output but also in terms of its capacity for performance under various loads.[3, 20]

ADAPTABILITY OF THE HEART

Cardiac Reserve. The heart is the central pump and source of energy of the circulatory system. Its normal function is characterized by a variability of performance remarkably adapted to changing demands. Thus the work of the heart may be increased sixfold during exercise, and its maximal output during running has been calculated as eight to ten times that of the resting state.[8]

Various other physiologic functions and pathologic states enhance the needs of the tissues for an increased blood flow and these augmented needs are satisfied by corresponding enhancement of the cardiac output. Thus, in health and disease the heart is potentially capable of a wide range of increased work performance beyond that required under basal conditions. The extent of this potentiality is known as *cardiac reserve*. A reduction in cardiac reserve is the first step on the path of cardiac failure. The severity of cardiac disability is measured by impairment of cardiac reserve.

THE LAW OF THE HEART

Our knowledge of the mechanisms of cardiac adaptation and the basis of cardiac reserve is dependent chiefly on animal experiments with the heart-

lung preparation[11] or other similar arrangements in which the essential variable circulatory factors are under the control of the experimenter. Broadly speaking, cardiac adaptation occurs as a response to variation in venous inflow into the heart, and to variation in resistance to outflow from the heart.[13, 6]

Cardiac Response to Increased Venous Inflow. In a controlled circulation, such as the heart-lung preparation, the arterial resistance (resistance to outflow) can be kept constant by a clamp on the aorta and the rate of the heart may be maintained constant by an excitatory stimulus whose rate is fixed. The inflow into the heart can be varied by infusions into the external jugular vein and the effects studied by observing the cardiac output, the size of the cardiac chambers and the intracardiac pressure curves.

If the venous inflow is increased, the intra-auricular and ventricular pressures rise. There is an increase in the diastolic size of the heart due to inability to eject immediately the increased amount of fluid. With the next few heart beats there is a progressive increase in cardiac output until this is equal to the increased inflow, and equilibrium is restored. Up to a certain "physiologic" limit, further increase in cardiac inflow results in continued increase in diastolic cardiac volume and this, in turn, in an augmented cardiac output.[15, 21] In this way the heart is able to adapt itself to respond adequately to an increased inflow of several hundred per cent. When the heart begins to fatigue, an augmented inflow causes an enlarged diastolic volume without a concomitant rise in cardiac output and the heart no longer ejects as much blood as it receives. This deficiency is denoted by a rise in venous pressure as well as by dilatation of the heart.

Cardiac Response to Increased Aortic Resistance. In similar experiments, the venous inflow can be maintained constant while the aortic resistance to outflow is increased by tightening the clamp on the aorta. In the subsequent cardiac contraction the left ventricle ejects less blood than formerly (i. e., less than it receives). The remainder is added to the constant venous inflow in diastole. The diastolic volume is thus increased. Pressure curves of the left ventricle show an elevation of initial tension and there is an increased force of contraction. The heart's output becomes larger until it ejects as much blood as it receives (i. e., the output returns to its original level), and equilibrium is restored. The cardiac output may be thus maintained even when the arterial resistance (pressure) is more than doubled.

Thus either an increased venous inflow or an increased resistance to cardiac outflow results first in an increased intracardiac tension and volume in diastole and then in an increased force of contraction.[14, 21] Consequently, despite the greater work imposed by these factors the heart either increases or maintains its output. Studies of the respiratory metabolism of the heart revealed that the increased force of contraction following enlargement of the diastolic volume was associated with the liberation of greater chemical as well as mechanical energy.[4, 18] *The observation that within physiologic limits a larger diastolic cardiac volume results in a greater energy of contraction and a greater amount of chemical change at each contraction has been termed the Law of the Heart (Starling).*[17] It is the fundamental principle governing the adaptability of the heart in coping with an increased venous inflow of blood to the heart or an increased resistance to its outflow.

However, with increasing inflow and increasing diastolic volume the crest of augmented cardiac output is reached and passed. Further increments in

venous return overload the heart and diminish the cardiac output. As the physiological fitness of the heart muscle is impaired, the point of overloading is reached earlier, i. e., with less quantities of venous return.

Cardiac Reserve. The greater energy of cardiac contraction accompanying an increased diastolic volume is analogous to the more forceful contraction of a strip of skeletal muscle, the greater the initial load, i. e., its initial length.[7] There has been some dispute as to whether the force of cardiac contraction is dependent on the initial tension,[5, 21] or on its initial length, as favored by Starling[17] and supported by the work of Anrep and Segall[1] and by Katz.[10] It may be that the initial diastolic tension of the heart is significant only insofar as it affects the length of the individual fibers. According to this concept, increased length of the fibers is associated with more forceful contraction because of the greater surface area available for chemical activity. The reserve of the heart is due to the reserve of the individual fibers and the latter, in turn, depends on their potential ability to undergo an increase in length. Up to a physiologic limit, this is accompanied by greater chemical and mechanical energy. Beyond this, increased length is accompanied by a diminution in the contraction.

Clinically, the cardiac reserve may be theorized as being the difference between the length of the cardiac fibers at rest and their length when the physiologic limit of stretch is reached. If as a result of cardiac disease the cardiac fibers are elongated so that they approach their physiologic limit when the individual is at rest, the cardiac reserve is diminished almost to the point of absence, and the heart may be unable to adapt itself adequately to the increased demands of physical exertion or other physiologic or pathologic strains.

Cardiac Tonus or Tone. There is considerable confusion in the definition and usage of the term, tone or tonus, as applied to the heart. Meek[12] has reviewed the evidence which indicates that cardiac tonus in the physiologic sense of a "sustained partial contraction" in diastole does not exist. Tonus has been defined as the degree of resistance to deformation, which according to Kabat and Visscher[9] represents the elasticity of the heart muscle. These authors consider the elasticity of the myocardium important in that it is a factor which determines the fiber length at any given filling pressure. A diminution in elasticity is correlated with decrease in the external work of the heart and eventually with cardiac failure.

Clinicians often employ the term, cardiac tone, in an ill-defined manner to indicate the quality of cardiac contraction. In this sense it is erroneously supposed that the more enlarged the heart, the poorer the tone. The tone of the heart muscle is also supposed to be indicated by the quality of the cardiac sounds. A useful concept of cardiac tone is that proposed by Starling,[17] i. e., the physiologic condition or fitness of the muscle fiber. Thus in the heart-lung preparation, when the heart deteriorates after several hours, its fibers must have a greater initial length to do the same work that it did when it was fresh. The tone or mechanical efficiency of the muscle fiber is said to be diminished. A heart with good muscular tone may undergo only a slight increase in diastolic volume in order to overcome an elevated arterial resistance, while a diseased heart with poorer tone ("physiologic fitness") may have to dilate much more to accomplish the same work. Starling's Law of the Heart[17] still applies to the fatigued heart in that a greater diastolic volume results in a greater energy of contraction. But the poorer the cardiac tone, the smaller the increment in

mechanical work effected by each unit increase in length of the cardiac fibers. Failure of the heart is thus characterized by a decreased capacity for doing work at a given fiber length or at a given diastolic volume.

Reflex Control of Cardiac Output. According to Starling's Law of the Heart the strength of ventricular contraction and the size of cardiac output are determined rather passively by changes in diastolic volume and the consequent degree of stretch of the myocardial fibers. Recently Stead and Warren[19] documented evidence to the effect that the ventricles are actively concerned in determining cardiac output. The cardiac output was found to be independent of wide variations in atrial pressure; it was found to increase with exercise or anxiety despite an increase in arterial pressure (i. e., despite an increased resistance to outflow). Furthermore a reduction in arterial pressure induced an immediate rise in cardiac output which appeared too rapidly for a humoral mechanism. They suggested that afferent stimuli arising from a reduction in arterial pressure, movement of the limbs during exercise or emotional thoughts produced a reflex stimulation of cardiac output according to variations in activity and needs. But the possibility is not excluded that such reflexes vary cardiac output not by direct modification of ventricular contraction but by first altering the venous inflow.

Factors Impairing Cardiac Output. An inadequate cardiac output may result from (1) a deficient venous return, (2) impaired cardiac contraction, (3) increased resistance to cardiac outflow.

1. Except momentarily, the output of the heart is equal to the venous return to the heart. Any reduction in venous return is rapidly mirrored in a corresponding reduction in cardiac output. The venous return may be gauged essentially by the amount of the circulating blood volume and by the speed with which this returns to the heart. Reductions in venous return usually follow a loss of circulating blood volume due to hemorrhage, loss of plasma or severe dehydration; or the venous return may be curtailed by mechanical obstructions to cardiac inflow. Occasionally the venous return falls to a completely inadequate amount following prolonged standing or in some individuals following a change from the recumbent to the erect position. This is due to a pooling of blood in the lower portions of the body because of a failure of sympathetic vasoconstrictor or other mechanisms to maintain an adequate venous return to the heart against the force of gravity. Not only the output of the heart as a whole but the output of each of its chambers is conditioned by the quantity of blood which is brought to it. Therefore, the inflow of blood and the output from the right or left ventricle tend to be diminished if there is an obstruction or stenosis of the tricuspid or mitral valves respectively.

2. Impaired cardiac contraction or a diminution in its physiologic fitness accounts for the great majority of instances of inadequate cardiac output and therefore of cardiac insufficiency. This is usually the result of a deficient blood supply (coronary insufficiency) or of diseases which damage the heart muscle or impair its physiologic efficiency. As we shall see, the *normal* cardiac muscle can long compensate for many serious loads imposed by cardiovascular or other diseases and still accommodate to the strains of vigorous activities. But with a reduction in myocardial strength and efficiency, overloading of the heart and inadequacy of output occur with progressively smaller stresses.

3. Increased resistance to outflow tends to reduce the cardiac output from the atria into the ventricles if there is an atrioventricular valvular stenosis,

or from the ventricles into the great vessels if there is an aortic or valvular stenosis. Hypertension with its increased peripheral resistance tends to reduce the output of the left ventricle.

Other factors which tend to reduce the cardiac output and thereby provoke heart failure include the valvular insufficiencies, which cause a regurgitation of some of the expelled blood. Thereby the effective blood flow to the tissues is less than the original ventricular output by the amount regurgitated. Similarly in shunts between large arteries and veins or between the right and left sides of the heart, the actual blood flow to the tissues is diminished by the quantity of shunted blood.

Finally the output may be inadequate in relation to inordinate requirements of the tissues because of excessive metabolism, e. g. hyperthyroidism, or because the normal quantity of blood is deficient in hemoglobin (anemias), vitamins (beriberi), or oxygen (advanced pulmonary emphysema). In the latter circumstances adequate amounts of oxygen, vitamins, etc., can be provided only by augmented cardiac outputs. In many cases, inadequacy of cardiac output is the result of a combination of factors, e. g., an increased demand of the tissues plus myocardial impairment in cases of anemia, or increased resistance to outflow plus myocardial damage in cases of hypertension with advanced coronary arteriosclerosis.

The following chapter is concerned with the compensatory mechanisms by which the heart and circulation long maintain an adequate output despite these factors.

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2

CARDIAC AND CIRCULATORY COMPENSATIONS

Compensation and Decompensation. A number of cardiac and circulatory compensations serve to restore an adequate cardiac output whenever the latter is threatened by disease. *When these adjustments succeed in maintaining an adequate blood flow without distressing symptoms, the heart and circulation are said to be in a state of compensation.*

Compensation may be complete or incomplete. Compensation is complete when the strain of the disease has been overcome, yet sufficient cardiac reserve remains to meet adequately the diverse demands of an active physical life. Incomplete compensation or cardiac decompensation denotes a substantial expenditure of the cardiac reserve in order to overcome the load imposed by disease; the remainder is such that unpleasant symptoms develop with slight or moderate activity. When the heart is adjusted to the disease factor but has no reserve for physical exertion, the heart is said to be compensated only at rest.

Types of Cardiac and Circulatory Adjustments. 1. The primary compensations concern the heart directly and include tachycardia, cardiac dilatation and cardiac hypertrophy.

2. When these primary compensations fail to restore or maintain an adequate cardiac output, renal retention of sodium and water increases the blood volume and thereby the venous return (Chapter 6). Within certain limits this tends to restore an adequate cardiac output (Chapter 1).

3. If the reduction in cardiac output is severe and occurs very rapidly (within a few hours), a significant augmentation of blood volume and venous return cannot be effected. Instead the deficient output is reapportioned so as to divert its major fraction to the vital brain and heart (Chapter 10).

4. A deficiency in cardiac output may be compensated also by metabolic, hematologic and other adjustments, e. g., an increase in erythrocytes in cases of congenital heart disease or chronic pulmonary disease, or increased extraction or utilization of the oxygen available in the transported blood.

CARDIAC COMPENSATION BY TACHYCARDIA

The cardiac output (minute volume of blood flow) is equal to the product of the stroke output and the cardiac rate. When the cardiac output must be

augmented to accommodate increased tissue demands due to exercise, this is accomplished by both an increase in rate and an increase in output. Of the two, the acceleration in rate is the less efficient mechanism. In the heart-lung preparation studied by Starling and Visscher it was found that a given unit of work was performed more efficiently, i. e. with a lesser consumption of oxygen, the slower the cardiac rate.[23] In athletes and subjects who have undergone a period of training, a physiologic enhancement of minute volume is accomplished essentially by an increased output per beat and to a lesser extent by an increased cardiac rate.[25, 4]

Similarly when the cardiac output is inadequate because of disease, it can be increased and restored to normal levels either by tachycardia or by augmented stroke output. As a rule tachycardia appears only as a transient compensatory mechanism, especially with sudden increases in cardiac demands. More efficient and more permanent compensation results from cardiac dilatation and hypertrophy which augment the total output by increasing the output per beat.

An accelerated heart rate (tachycardia) appears not only as a compensation for an inadequate cardiac output but also as a result of a variety of unrelated conditions. When a deficient output is compensated by dilatation and hypertrophy, the heart rate is usually normal. However, muscular exercise induces a greater acceleration of the heart rate and greater persistence of such tachycardia at the conclusion of activity than is found in the normal person. When the cardiac output is uncompensated despite cardiac dilatation, hypertrophy and other mechanisms (i. e., in heart failure), tachycardia is often present despite minimal activity. Tachycardia is the major cardiac compensation when the stroke output cannot be increased either because of severe acute myocardial injury or because of a sharply reduced blood volume and venous inflow into the heart (shock).

The compensatory value of tachycardia is limited by the shortening of diastole and consequent reduction in ventricular filling, as the rate increases. Experiments with the heart-lung preparation have shown that beyond the rate of 180 beats per minute, the reduction in ventricular filling and ventricular output becomes so great that further increases in cardiac rate actually reduce the total minute volume.[8]

Pathogenesis of Compensatory Tachycardia. A compensatory increase in heart rate is effected by various mechanical, chemical and nervous stimuli which diminish the tone of the cardioinhibitory center and vagus nerve and increase that of the cardioaccelerator centers and accelerator fibers in the sympathetic nerves.[12, 20] A fall in aortic and carotid arterial pressure, as the cardiac output is reduced, inhibits the carotid sinus and aortic depressor nerves and reflexly reduces vagal tone.[9, 13, 27] At the same time an inadequate output tends to be associated with stasis and elevation of pressure in the vena cava and right atrium. This may stimulate receptors which reflexly cause cardiac acceleration, by inhibiting the vagus and stimulating the accelerator center and fibers (Bainbridge reflex).[3, 16] (The site and significance of this reflex have been amplified by Nonidez[21] and questioned by De Graff and Sands[5] and by Anrep and Segall.[2]) The secretion of epinephrine and the accumulation of metabolites as the output falls may also be concerned in effecting a compensatory tachycardia. The exact mechanisms are uncertain.

CARDIAC DILATATION

Cardiac dilatation denotes an increased capacity of the cardiac chambers. Its compensatory action is explained by the Law of the Heart (p. 3). Since the length of the muscle fiber determines "the mechanical energy set free" or the strength of contraction, dilatation of the heart by elongating myocardial fibers results in more work and an increased stroke output. The greater effectiveness is probably due to the larger surface area of elongated fibers available for active physicochemical processes. The extent of cardiac dilatation necessary to compensate a given load due to cardiovascular disease increases as the load increases or as the physiologic fitness of the myocardium diminishes.

Cardiac enlargement, chiefly due to dilatation of its chambers, is the commonest manifestation of any cardiovascular disease which tends to impair the cardiac output. Furthermore the dilatation is localized or most conspicuous in that cardiac chamber, or even in that portion of a chamber, which is subjected to the greatest strain. The frequent observation that individuals with cardiac enlargement are long able to maintain good circulatory function, supports the concept that cardiac dilatation is a mechanism for compensating cardiovascular lesions which tend to interfere with an adequate cardiac output.

Cardiovascular Diseases and Compensatory Dilatation. Cardiac dilatation may result from (1) mechanical lesions, (2) myocardial lesions or often a combination of both.

1. *Mechanical lesions* tend to increase the diastolic volume and thereby cause cardiac dilatation by (a) increasing the venous return to the heart, e. g., in cases of arteriovenous aneurysm; (b) increasing the resistance to outflow from one of its chambers, e. g., mitral or aortic valvular stenosis or hypertension; (c) permitting a reflux of blood into a chamber after it is ejected, e. g., in aortic valvular insufficiency.

2. *Myocardial lesions* tend to impair cardiac contraction and diminish cardiac output while the inflow is temporarily unchanged. This causes an increase in the diastolic volume and cardiac dilatation (e. g., myocardial infarcts secondary to coronary occlusions, rheumatic myocarditis, etc.).

Most frequently cardiac contraction is impaired by coronary artery disease or rheumatic myocarditis at the same time that a mechanical strain is imposed by hypertension or valvular defects. Whether due to a mechanical lesion or to an impaired myocardial contraction, dilatation results from an inability of the affected chamber to expel an increased venous return or to eject a normal venous return against an abnormal obstruction or a regurgitant stream.

When heart failure occurs, the compensatory mechanisms may be said to have failed in restoring an adequate cardiac output. However, they continue to operate. If a moderate degree of cardiac dilatation effects the needed increase in cardiac output, this remains unchanged so long as the status of the myocardium and the mechanical lesion remain unchanged. If the cardiac output is definitely inadequate despite a given degree of dilatation (i. e., cardiac failure ensues), the heart continues to dilate in a futile compensatory effort. The enlarged circulating blood volume which is an essential feature of chronic heart failure contributes significantly to the increased diastolic volume and cardiac dilatation. Thus the most rapid and pronounced degrees of cardiac enlargement are observed in the failing heart.

CARDIAC HYPERTROPHY

Cardiac hypertrophy denotes an increase in the weight of the heart associated with an enlargement of the individual muscle fibers. Pseudo-hypertrophy and false hypertrophy are terms that have been applied to hearts whose weights are increased, not by enlargement of muscle fibers, but by edema as in beriberi, or by glycogen infiltration as in von Gierke's disease.

Cardiac hypertrophy may sometimes be surmised from clinical and roentgenologic studies, especially angiocardiography, but essentially it is a postmortem diagnosis based on the weight of the heart, the thickness of chamber walls or gross and histologic examination. Hypertrophy of individual chambers may be similarly determined by dissection and by weighing.[10, 17] Normally the heart weighs 0.43 per cent of the body weight in men, 0.40 per cent in women.[22] The heart weight is directly proportional to muscular development and therefore in obese individuals the percentage of heart to body weight is less than in muscular persons. A heart weighing more than 400 gm. in an adult male or more than 375 gm. in an adult female is practically always hypertrophied; as a rule, weights exceeding 350 gm. and 300 gm. respectively denote cardiac hypertrophy. At birth the percentage of heart weight to body weight averages 0.62 per cent for males and 0.55 per cent for females. In old age there is usually some atrophy of the heart. The normal thickness of the left ventricle midway between apex and mitral valve is 10 to 12 mm.; that of the right ventricle midway between apex and pulmonary valve is 3 to 4 mm.

The determination of dilatation and hypertrophy of individual segments of the various chambers, at necropsy examination, has been described by Kirch.[15]

The Compensatory Nature of Cardiac Hypertrophy. That cardiac hypertrophy is a compensatory mechanism is concluded from the experimental, pathologic and clinical observations that: (1) it appears when there is a disturbance which tends to interfere with normal cardiac function; (2) it is localized in the chamber or chambers affected by the disturbance; (3) after its development normal cardiac function is frequently restored.

Experimental evidence indicates that the hypertrophied heart not only maintains the normal circulation despite a cardiovascular lesion, but also retains an adequate reserve for unusual circulatory demands. Hasenfeld and Romberg[7] produced aortic insufficiency in rabbits' hearts and observed the development of cardiac hypertrophy. They concluded that the reserve strength of these hearts was not impaired and that cardiac hypertrophy is a sign of increased strength. Similarly Wolfer[29] observed that rabbits' hearts which had become hypertrophied after experimentally produced aortic stenosis or repeated injections of epinephrine responded perfectly to increased physical demands.

From clinical and pathologic studies it is clear that cardiac hypertrophy is not incompatible either with normal activity or with long life. I have observed individuals who in spite of their enormous hearts associated with aortic stenosis or insufficiency have engaged in the severest athletics and lived a normal span of life. For practical purposes no distinction could be made between the physical capabilities of these individuals and those of persons with normal hearts.

The hypertrophied cardiac muscle contracts more strongly at a given diastolic volume than before it was hypertrophied. In other words, because of their

greater size the hypertrophied muscle fibers are capable of developing more energy with each contraction. Any increase in diastolic volume is accompanied by a much greater increase in the force of contraction than could occur in the heart without hypertrophy. In addition, the hypertrophied heart is capable of a greater maximum energy of contraction so that its reserve may be comparable to that of the normal heart. It is generally believed that with a given cardiac or vascular lesion the hypertrophied heart is more capable of compensation than if it were not hypertrophied. However, this does not indicate that the hypertrophied heart is as efficient or will last as long as the normal heart.

Relation of Cardiac Dilatation and Cardiac Hypertrophy. Cardiac hypertrophy and cardiac dilatation are both compensatory mechanisms. Cardiac dilatation is the immediate response of the heart when it must expel a constant volume of blood against an increased resistance or an increased volume of blood against an increased resistance or an increased volume against a constant resistance. While the dilated heart overcomes these obstacles, it does so with less mechanical efficiency than the normal heart and by encroaching on the cardiac reserve. Cardiac hypertrophy is a more efficient compensatory response to similar cardiovascular disturbances, but it requires more time to develop. The hypertrophied heart is stronger and more efficient than the dilated heart because it can accomplish more work with the same initial (diastolic) length of the muscle fibers.

Experimental and pathologic evidence indicates that cardiac dilatation and hypertrophy are responses to the same stimuli, dilatation occurring immediately and hypertrophy after some time and probably as a result of unknown physicochemical changes induced by the primary dilatation. The lengthening of muscle fibers associated with cardiac dilatation allows a greater surface area for the diffusion of metabolites which may aid in the growth of the fibers. Horvath[14] first emphasized that the development of cardiac hypertrophy was dependent on and preceded by cardiac dilatation. Eyster, Meek and Hodges[6] showed that following experimental aortic insufficiency and aortic stenosis in dogs, dilatation occurred rapidly and reached a maximum in three to six days. Hypertrophy developed subsequently and was maximal only after one hundred days.

In human pathology cardiac dilatation and hypertrophy are almost always associated and localized in the same portions of the heart. This indicates that they are responses to the same stimulus. Sometimes it can be demonstrated that dilatation precedes hypertrophy. Thus in cases of acute glomerulonephritis, death from cardiac failure occasionally occurs in the first week of the illness. The hearts show definite dilatation but no hypertrophy. On the other hand, if death occurs after a month, a significant degree of hypertrophy is present.

Pathogenesis of Cardiac Hypertrophy. Many theories have been proposed to explain the development of cardiac hypertrophy.[28, 11]

1. *The theory of work hypertrophy* imputes cardiac hypertrophy to an increase in the work of the heart. Observations in animals indicate that the size of an animal's heart increases in proportion to the amount of activity necessitated by its mode of life and that cardiac hypertrophy can be induced by exercising dogs.[24] Clinical and pathologic observations disclose that hypertrophy of a chamber occurs when its work is increased in compensation for a valvular or circulatory abnormality.

2. *The nutritional theory* attributes cardiac hypertrophy to a defective blood

supply, and is based largely on the development of hypertrophy in clinical and experimental anemia and the belief that cardiac hypertrophy in arteriovenous aneurysm and aortic insufficiency is due to a deficient coronary circulation.[18]

3. *The injury theory* suggests that cardiac hypertrophy is a reaction to tissue injury which acts as a pathologic nutritive stimulus.[1, 6]

4. *The muscular stretch theory* suggests that the fundamental cause of hypertrophy is the stretching of muscle fibers.[14] This is not necessarily contradictory to the above theories but more clearly and precisely defines their application. Stretching of myocardial fibers results whenever the diastolic volume and pressure are increased by enhanced inflow, impaired myocardial contraction or increased resistance to outflow. This is the stage of cardiac dilatation.

The lengthening of muscle fibers results in a greater surface area for an unchanged mass of muscle. This permits a relatively greater nutritive diffusion surface between blood and fiber and therefore leads to the fiber's growth. In due time the dilated fibers become hypertrophied. This explains the development of cardiac hypertrophy following dilatation in cases of valvular and vascular lesions as well as in instances of myocardial disease. Progressive heart failure is a potent factor in pronounced cardiac hypertrophy because it is responsible for a progressive increase in diastolic volume and consequent muscle stretch. On the other hand increased work of the heart does not cause hypertrophy if the additional work is due exclusively to tachycardia while the stroke output is not enhanced, as in most cases of uncomplicated hyperthyroidism.

Reversibility of Cardiac Dilatation and Hypertrophy. Roentgenologic observations have disclosed that cardiac enlargement (dilatation and hypertrophy) is reversible even when it has been present for years, provided that the causative disturbance is abolished or alleviated.[26] Cardiac enlargement has been seen to diminish with regression of the symptoms of heart failure, and to disappear completely or diminish with (a) subsidence of acute glomerulonephritis, (b) correction of anemia, (c) surgical correction of an arteriovenous aneurysm, patent ductus arteriosus, coarctation of aorta or hyperthyroidism with heart failure, (d) adequate thyroid administration in myxedema heart disease, (e) vitamin B and protein therapy in beriberi heart disease, (f) sympathectomy in hypertensive heart disease.

That cardiac hypertrophy as well as dilatation is reversible is indicated by the case of arteriovenous aneurysm due to congenital cavernous hemangioma reported by Matas and Heninger.[19] The greatly enlarged heart in this case was restored to normal size, as determined roentgenologically, following surgical removal of the hemangioma. Because cardiac enlargement had been present at least four years, Matas and Heninger[19] believed there must have been hypertrophy as well as dilatation and that hypertrophy, like dilatation, could regress when the cause was removed. Electrocardiographic and roentgen ray studies of the heart in hypertensive heart disease before and after sympathectomy also indicate that ventricular hypertrophy is reversible (p. 863).

CIRCULATORY COMPENSATION BY INCREASED BLOOD VOLUME AND VENOUS RETURN

When cardiac dilatation and hypertrophy, with or without tachycardia, are no longer capable of maintaining an adequate cardiac output, the cardiac reserve

is largely expended and there is an insufficient blood supply to the tissues. This deficiency in blood flow may occur only with physical exertion or, in extreme cases, even with the patient at rest. At this stage, extracardiac compensatory mechanisms are invoked and these may partially or completely restore the cardiac output for a variable period.

Briefly, a diminished cardiac output causes a deficient renal blood flow which in some manner results in a retention of sodium and water and a corresponding increase in the circulating blood volume. The latter augments the venous return and thereby stimulates the failing ventricle to restore an adequate output according to the Law of the Heart. This compensatory mechanism will be discussed in detail in the chapter on the pathogenesis of congestive heart failure (Chapter 6).

CIRCULATORY COMPENSATION BY REDISTRIBUTION OF A DIMINISHED CARDIAC OUTPUT

A significant compensatory increase in blood volume can be effected only over a period of days or weeks. Furthermore this compensatory mechanism is most effective when the reduction in cardiac output is relatively small (10 to 20 per cent). When a diminution in cardiac output occurs rapidly (in a few hours) and is of pronounced degree (25 per cent or more), a restoration of cardiac output cannot be rapidly accomplished by an increased blood volume or by any other means. A slight immediate compensatory increase in circulating blood volume may occur as a result of an intravascular influx of extracellular or intracellular fluid, but this is clinically insignificant.

To preserve the life of vital organs such as the brain and heart, the little blood flow available is redistributed in such a way as to divert most of it from the periphery and splanchnic areas to more vital structures. This is probably accomplished in large measure by reflex inhibition of carotid sinus and aortic depressor tone, by stimulating the secretion of epinephrine and perhaps by direct anoxemic stimulation of the vasomotor center—all of which produce sympathetic vasoconstriction, especially of the skin and splanchnic viscera. This compensatory mechanism is discussed more fully in the section on the pathogenesis of acute circulatory failure or shock (Chapter 10). Vasoconstrictive redistribution of blood also occurs in the more chronic and milder forms of deficient cardiac output, but it is less important than the mechanism of increased blood volume.

Relation of Compensatory Mechanisms to Clinical Manifestations of Cardiac and Circulatory Dysfunction. Except in occasional instances of extreme and acute reduction of cardiac output, symptoms of circulatory deficiency are not due directly to the inadequate output. In cases of irreversible and fatal shock, syncope and sudden death, the compensatory mechanisms have failed to maintain an adequate output to supply vital organs, notably the brain; temporary unconsciousness or death is actually due to the deficient output. As a rule, however, despite serious cardiovascular disease, the blood flow to the brain and heart is adequately maintained by the enumerated compensations. Under these circumstances the clinical manifestati ns of the cardiovascular diseases which have threatened the adequacy of the circulation are determined not by insufficient output but by the compensations which restore that output.

In the mildest cases a falling cardiac output is adjusted by cardiac dilata-

tion and hypertrophy which are denoted clinically by signs of enlargement of the heart. The patient is said to have compensated heart disease. The compensations (cardiac dilatation and hypertrophy) are the evidence of cardiovascular disease. Although beneficent in their effect on cardiac output, they are abnormal in that they denote the existence of a serious disease which requires cardiac compensation, and in that they expend some of the reserve power of the heart. Furthermore the enlarged hypertrophied heart has increased muscle mass without a corresponding increase in the number or size of the blood vessels. This disparity predisposes to myocardial inefficiency and heart failure (p. 49). Thus cardiac enlargement may be considered as a compensatory process (Chapter 2), as an evidence of cardiovascular disease (Chapter 3) and as a mechanism predisposing to heart failure (Chapter 4).

When extracardiac compensations must be invoked to maintain an adequate cardiac output, clinical evidence of cardiac or circulatory failure appears. Here also, the clinical manifestations are not the direct result of a deficient cardiac output but of the compensatory mechanisms which attempt to restore that output. Since heart failure or circulatory failure is defined in terms of clinical phenomena, and these are produced by circulatory compensations and not by deficient output, heart failure may be present despite an adequate output. The deficient output initiates the compensatory mechanism but the compensatory mechanism produces symptoms.

When the extracardiac compensation is chiefly that of increased circulating blood volume, the resulting clinical phenomena are those of chronic circulatory or cardiac failure. When the extracardiac compensation is chiefly that of redistribution of a greatly diminished output, the compensatory process leads to the clinical phenomena known as acute circulatory failure (shock). Syncope and death are often manifestations of acute circulatory failure, and are actually due to the deficient output itself; in such instances the compensation of redistribution of blood to the vital brain has failed temporarily or permanently.

Accordingly the following classification of circulatory failure is proposed. Heart failure and circulatory failure are used synonymously because failure of the heart cannot persist without failure of the circulation and vice versa.

CLASSIFICATION OF CIRCULATORY FAILURE

I—Chronic circulatory failure (congestive heart failure)
- A—Left-sided heart failure
- B—Right-sided heart failure
- C—Combined left- and right-sided failure
- D—Heart failure due to prolonged or chronic interference with inflow
  1. Constrictive pericarditis
  2. Persistent severe tachycardias
- E—Heart failure associated with increased venous return (high output failure)
  1. Arteriovenous aneurysm
  2. Chronic severe anemias
  3. Beriberi
  4. Hyperthyroidism
  5. Pulmonary emphysema
  6. Paget's disease

II—Acute circulatory failure (Chapter 10)
- A—Shock
- B—Syncope
- C—Sudden death

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3

ENLARGEMENT OF THE HEART

This chapter is concerned with cardiac dilatation and hypertrophy, not as compensatory mechanisms, but as evidences of myocardial, valvular or circulatory disease. In clinical discussions, the term cardiac enlargement is employed to signify dilatation and/or hypertrophy, because the determination of the presence and degree of each of the latter is extremely difficult.

Enlargement of the heart occurs with most of the serious forms of heart disease. However, coronary arteriosclerosis and narrowing, or even coronary occlusion, may be unaccompanied by cardiac enlargement because an adequate output is maintained despite the coronary and myocardial disease. Constrictive pericarditis is associated with a small or normal-sized heart because the obstruction to venous return prevents an increase in diastolic volume and diastolic stretch which is the stimulus to enlargement. The heart is not enlarged in the circulatory disturbances associated with uncomplicated shock because in these instances also there is a small venous return and no increase in diastolic volume. Finally in the early stages of hypertension, valvular and myocardial diseases in which there is relatively little strain on the heart, the degree of enlargement may be too slight to demonstrate with assurance, especially since there is a relatively large range in the size of the normal heart.

Clinical recognition of cardiac enlargement depends chiefly on physical and roentgenologic examination. The presence of cardiac enlargement may also be suggested or confirmed by the electrocardiographic findings. Cardiac enlargement not only denotes the presence of cardiac disease but also, because of its characteristic localizations, may indicate the exact nature of the cardiac lesion.

PHYSICAL SIGNS OF CARDIAC ENLARGEMENT

The chief physical signs of cardiac enlargement are displacement of the apex beat as determined by inspection and palpation or displacement of the cardiac borders as determined by percussion.[8, 70] As a rule, cardiac enlargement is present when the maximum apical impulse is situated lateral to the midclavicular line, or more than 10 cm. from the midsternal line in the fifth left intercostal space, or below the level of the fifth intercostal space.[65] Cardiac displacement due to bronchopulmonary lesions may similarly affect the position of the apical impulse. In many persons it is difficult or impossible either to see or clearly to feel the apex beat.

Cardiac enlargement may also be denoted by an accentuated or diffuse apical

impulse. The accentuated apical impulse due to hypertrophy of the left ventricle was considered characteristic of aortic insufficiency by Bard,[5] who termed the pulsation "choc en dome." Enlargement of the right ventricle may be suggested by a pronounced epigastric pulsation. A precordial bulge is often observed in children with cardiac enlargement due to rheumatic or congenital cardiac disease. Distinctive pulsations of the chest wall have been associated with individual cardiac lesions.[15]

Percussion discloses cardiac enlargement or displacement if cardiac dullness extends beyond 10 cm. to the left of the midsternal line in the fifth interspace.[33, 49] It may denote either left or right ventricular enlargement. If cardiac dullness extends more than 4 cm. from the midsternal line in the third left interspace, there is probably enlargement of the left atrium, dilatation of the pulmonary artery or possibly enlargement of the pulmonary conus of the right ventricle. The value of percussion of the right side and base of the heart is more limited except in cases of gross enlargement. The accuracy with which cardiac enlargement can be discovered by percussion is impaired in very obese individuals, in those with a very muscular chest wall, in subjects with pronounced pulmonary emphysema and in women with large breasts. Despite the imperfections of these physical methods,[42, 54, 46] the physician should refine his skill in them because they are the only means of discovering cardiac enlargement at the bedside, when the patient is too ill, or facilities are not available for roentgen ray examination.

ROENTGENOLOGIC EXAMINATION OF THE HEART

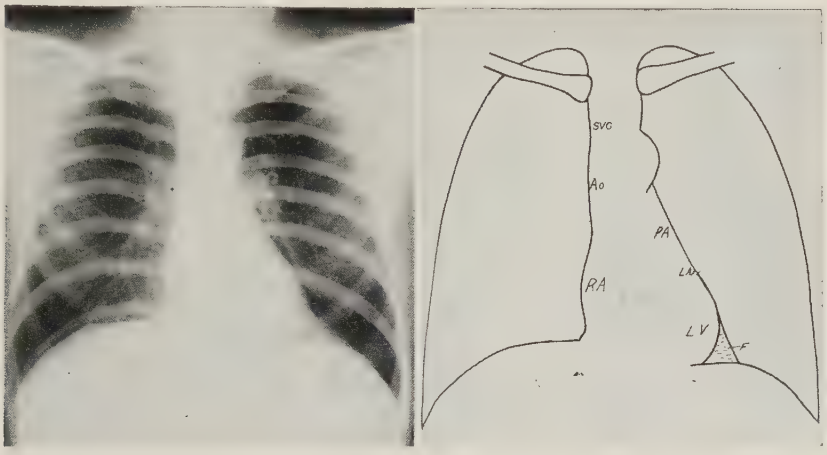
Roentgenologic examination of the heart is the most reliable method of determining cardiac enlargement. Not only does it provide an accurate outline of the projected cardiac borders, but it reveals also the volume of the heart and its vascular extensions, the relative size of the individual chambers, and the character and extent of the cardiac pulsations. By rotating the patient, the examiner may view the heart from every angle. Permanent objective records of the cardiac silhouette may be made on films or tracings. Often single examinations are inconclusive as to the presence of cardiac enlargement. But when permanent records are made at intervals, a comparison of these records may reveal significant changes in size indicative of cardiac enlargement. Serial records also provide useful information as to the progression and course of various cardiac diseases. Thus, roentgenologic examination reveals the cardiac size and conformation of the heart throughout the progressive stages of given cardiac affections, while postmortem examination discloses only the end result of such diseases.

The size of the heart and the presence and localization of cardiac enlargement may be determined by fluoroscopy, orthodiagraphy and teleoroentgenography. In special instances, especially in cases of congenital heart disease (p. 684) and in distinguishing cardiac enlargement from extracardiac masses, angiocardiography[56, 68] has proven valuable. Kymography[31, 26] and electrokymography[29] may aid in distinguishing cardiac enlargement from pericardial effusion and ventricular aneurysm. Technical details as well as findings in various cardiac diseases may be found in the excellent monographs of Assmann,[3] Vaquez and Bordet,[74] Zdansky,[84] Roesler,[57] Laubry et al.[43] and Schwedel.[62] The anatomical basis for the roentgenologic silhouette of the heart is presented in a monograph by Koch and Wieck.[40]

The Normal Cardiac Silhouette

For purposes of simplification and standardization we usually employ three views which yield the maximum information as to the shape, size and (by fluoroscopy) the pulsations of the heart. These views are the anteroposterior, the right oblique anterior and the left oblique anterior. Occasionally the lateral view is also of value.

The Anteroposterior View. About two thirds of the cardiac shadow is to the left, and one third to the right of the midline (Fig. 1). The *right border* is composed of three contours, which from above downward are: (1) The *innominate vein* and its continuation into the superior vena cava. (2) The *superior vena cava* or, in older individuals, the *ascending aorta.* The shadow of the ascending aorta may be seen within that of the superior vena cava even



A B

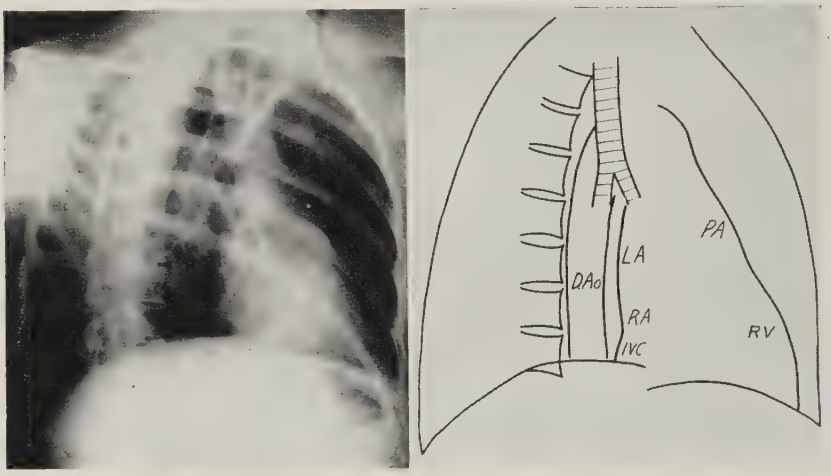
Fig. 1. *A,* Normal cardiac silhouette. Male, aged 45. Posteroanterior view.
B, Diagram of *A.* RA = right atrium, Ao = ascending aorta, SVC = superior vena cava, LV = left ventricle, LAp = left atrial appendage, PA = pulmonary artery, F = apical fat pad.

when it does not reach the right border of the heart. (3) The *right atrium,* which forms a well-curved contour separated by a slight indentation from the superior vena cava above it, and is the largest salient of the right border of the heart. Occasionally there may be seen a small portion of the shadow of the inferior vena cava as it enters the lower region of the right atrium.

The *left border* also has three main contours, which are formed from above downward by: (1) The *aortic arch* continuing into the descending aorta. (2) The *pulmonary salient.* This is composed of the pulmonary artery and its left main branch. The left auricular appendage may appear below the pulmonary artery. This middle segment is sometimes referred to as the waist of the heart because it is distinctly indented as compared with the bulge of the third contour below it. The junction of the pulmonary salient and the latter contour is denoted by a reversal in direction of pulsation. (3) The *left ventricle.* This forms a prominent convex contour, which extends well into the left pulmonic field and curves downward and back toward the midline to cross the shadow of the left leaf of the diaphragm. In the left cardiodiaphragmatic angle there is often a

faint triangular shadow which represents a pad of fat in a fold extending from the pericardium to the mediastinal and diaphragmatic pleura. Failure to recognize the cause of this shadow may lead to error in measuring the cardiac size.

The Right Anterior Oblique View. The patient is rotated anteriorly so that his right shoulder is turned toward the screen. The angle formed by the shoulders with the screen should be about 30 to 40 degrees for study of the aorta, or 50 to 60 degrees for study of the left atrium. The patient's right hand is placed on his head and the dorsum of his left hand is placed on the crest of the ileum, the left elbow being drawn forward at the same time. The *anterior border* of the cardiac silhouette in this view (Fig. 2) is formed in its upper third by (1) *the ascending aorta and arch;* and in its lower two thirds by (2) *the pulmonary artery and right ventricle.* With only moderate rotation (30°) the left ventricle forms the lower anterior contour.



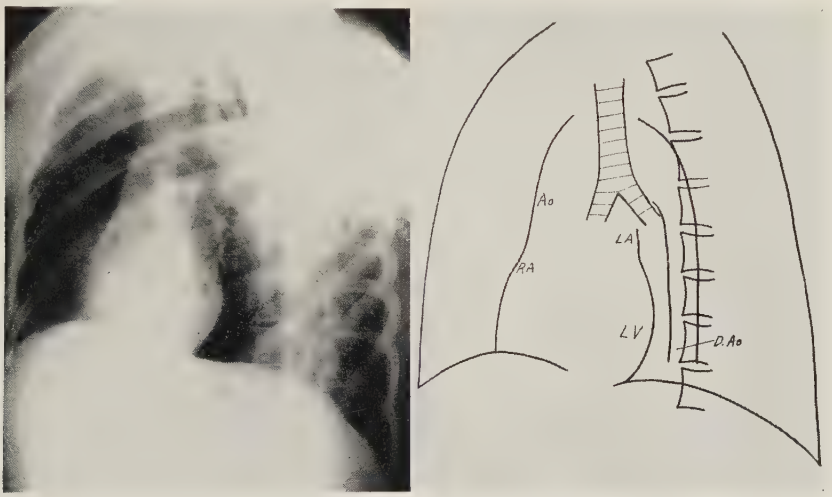
A B

Fig. 2. *A,* Normal heart. Same as in Fig. 1. Right anterior oblique view.
B, Diagram of *A.* IVC = inferior vena cava, DAo = descending aorta, RV = right ventricle, LA = left atrium. Other abbreviations as in Fig. 1*B.*

The *retrocardiac space* should be clear at an angle of 30 to 40 degrees, and its clarity enhanced by increasing the angle of rotation, or by making the patient inspire deeply. The posterior aspect of the cardiovascular silhouette from above downward reveals the following structures: (1) *The trachea and left main bronchus* form a transparent band, overlying which is the right branch of the pulmonary artery and the superior vena cava. (2) *The descending aorta.* (3) *The left atrium,* which is slightly convex and forms the major portion of the posterior cardiac border. (4) *The right atrium* with the shadow of the inferior vena cava entering it.

The Left Anterior Oblique View. The patient is rotated anteriorly so that his left shoulder is toward the screen. The angle of rotation is 40 to 50 degrees for study of the aorta, and 50 to 60 degrees for study of the ventricles. The patient's left hand is placed on his head, his right hand on his right hip, and his right elbow drawn forward. This view is especially valuable for the study of the aorta, the inflow tract of the right ventricle, the left atrium, and the left ven-

tricle.[52, 51] The *anterior aspect* of the cardiovascular silhouette in this position (Fig. 3) is composed of three contours, which from above downward represent: (1) *The innominate vein and superior vena cava.* (2) *The ascending aorta.* (3) *The right atrium.* The right atrial appendage reaches the anterior contour of the upper end of the right atrium. According to angiocardiographic studies the right ventricle may constitute the lowermost portion of this contour, but most often it is obscured by the right atrium.[67] In this view also, the aorta may be followed craniad where it arches over the top of the cardiovascular silhouette and continues into the descending aorta, which merges with the shadow of the spine. Below the aortic arch is the bifurcation of the trachea, forming a transparent region known as the aortic window, traversed by the pulmonary artery.[55]



A B

Fig. 3. *A,* Normal heart. Same as in Figs. 1 and 2. Left anterior oblique view. *B,* Diagram of 3*A*. Abbreviations as in Fig. 2*B*.

The dorsal aspect is formed in its upper third by (1) *the left atrium,* and in its lower two thirds by (2) *the left ventricle.* The cardiac shadow posteriorly should be separated from the spine if the patient is rotated 45 degrees or more. The lower border of the cardiac silhouette is important in this view as it may reveal enlargement of the inflow tract of the right ventricle. The anterior two thirds or three quarters of this border represents the diaphragmatic surface of the right ventricle. The posterior quarter is formed by the left ventricle. Between these two there is often a small indentation which is best seen during deep inspiration and in systole. This indentation was said to represent the interventricular sulcus[51] but it does not correspond to the interventricular septum as seen by angiocardiography.[67]

As the patient is rotated into a lateral position, the anterior contours from below upward are the right ventricle and its conus, the pulmonary artery and the aorta. Posteriorly the left ventricle forms the lower contour and the left atrium the upper.

The Normal Cardiac Size and Cardiac Enlargement as Determined by Roentgenography

The discovery of cardiac enlargement by means of roentgenologic examination requires a knowledge of the normal size of the heart as projected by roentgen rays. Actually, we cannot directly measure the volume of the heart because only one plane of this solid object is presented. But attempts have been made to calculate both the surface area and the cardiac volume from various linear measurements of the cardiac shadow. Unfortunately, the range of normal values, even within groups which are uniform with respect to age, sex, height and weight, is so great that only conspicuous abnormalities of cardiac size can be recognized with certainty from these measurements. Furthermore, cardiac enlargement is often limited to one chamber or a portion of a chamber, leaving

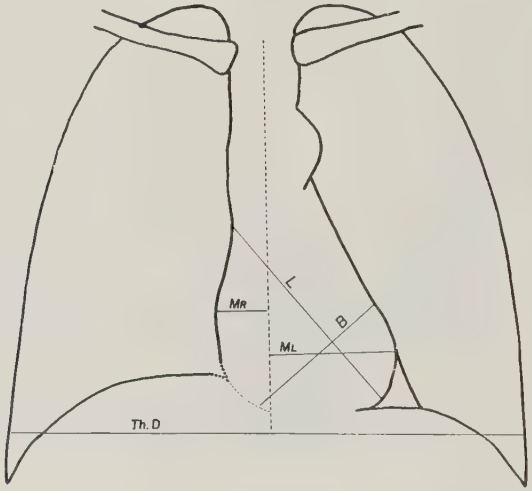


Fig. 4. Cardiac diameters of normal heart in Fig. 1. MR = 4.1 cm., ML = 7.3 cm., TD (transverse diameter) = MR + ML = 11.4 cm. Internal thoracic diameter Th.D = 30.5 cm., L (long diameter) = 13.4 cm., B (broad diameter) sum of perpendiculars to L = 10.4 cm.

the total cardiac area or certain commonly used linear dimensions of the heart within normal limits.

For these reasons, there is a tendency to dispense with detailed measurements to determine enlargement. More emphasis is being placed on acquiring skill in recognizing abnormalities in cardiac size and contours simply by viewing the heart and its component parts in various positions. The chief purpose of recording cardiac measurements is to compare records taken at different times in order to discover progressive changes. It should be emphasized that such comparisons are unreliable unless the technical conditions, such as the target film distance, the centering of the patient with respect to the target and the film, the position of the chest and the diaphragm, and the phase of the respiratory and cardiac cycle, remain identical.

The Transverse Diameter. The commonest measurement in teleoroentgenograms or orthodiagrams is that of the *transverse diameter* (T or H). This is the sum of the perpendicular from the outermost point on the right cardiac border

to the midsternal line (MR) and the perpendicular from the outermost point of the left cardiac border to the midsternal line (ML) (Fig. 4). In the erect

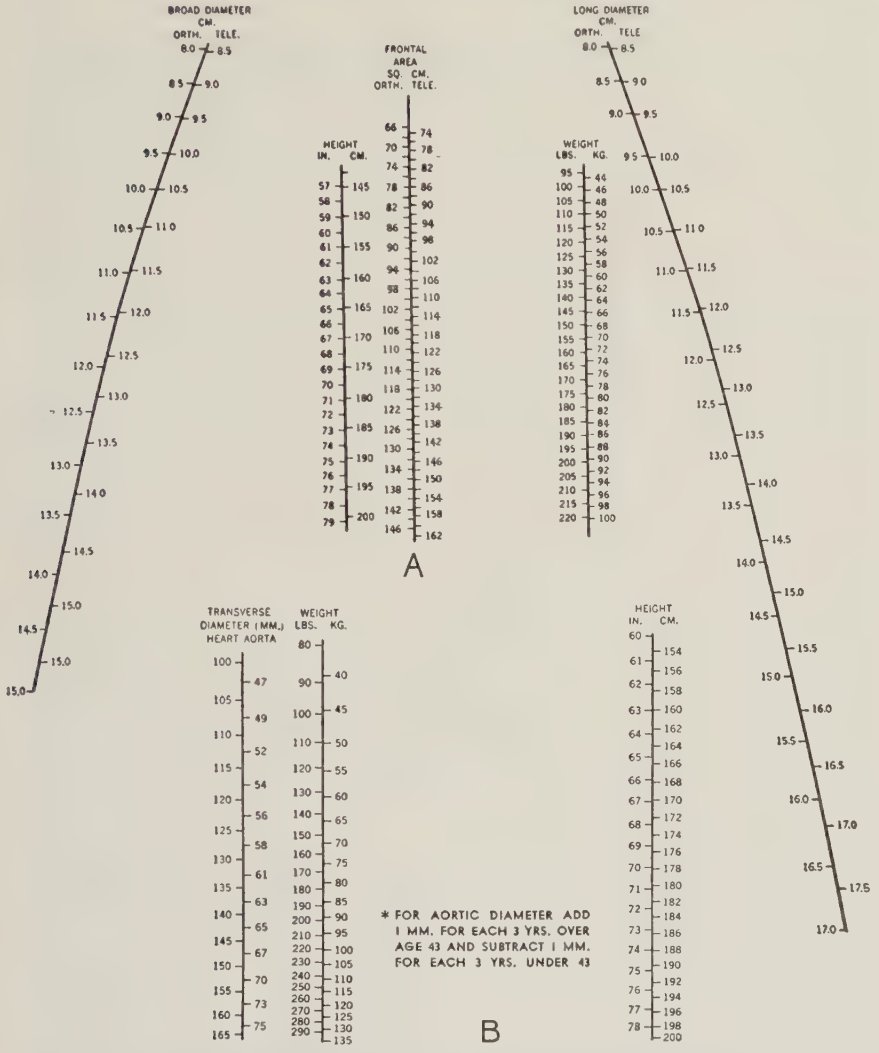


Fig. 5. *A*, Nomogram for prediction of frontal area of cardiac silhouette and for actual area from long and broad diameters (Ungerleider—Gubner). Extension of line connecting height and weight gives predicted area and connecting long and broad diameters gives actual area.

B, Prediction table for transverse diameter of cardiac silhouette (Ungerleider—Gubner). The theoretical transverse diameter of the heart (left column) is obtained by extension of line connecting height and weight. Actual transverse diameter exceeding predicted value by more than 10 per cent is abnormal.

position of the body, the transverse diameter averages between 10 and 13 cm. but even greater variations occur normally.

The cardiothoracic ratio has often been used as an index of cardiac enlargement.[13] This is the ratio of the transverse diameter of the heart to the internal

diameter of the chest at its widest point just above the level of the dome of the diaphragm. If the cardiothoracic ratio significantly exceeds 50 per cent it is assumed there is cardiac enlargement. This is only a rough guide as the relationship varies considerably.[12]

On the other hand, the normal transverse diameter has been shown to bear a definite relation to the surface area or the weight and height of the individual. Hodges and Eyster[32] have constructed tables in which the normal transverse diameter of the heart, as obtained on orthodiagrams, is predicted with reasonable accuracy on the basis of height and weight. Edeiken and Wood[16] indicated that these figures may be about 10 per cent too high for young male adults. Similar tables for children have been prepared by Gordon and Adams,[25] and roentgenologic studies of the size of the heart in childhood have been reported by Taussig and Goldenberg.[69] Ungerleider and Clark[72] constructed tables for predicting the transverse diameter of the heart silhouette, as obtained on teleoroentgenograms (instead of orthodiagrams as utilized by Hodges and Eyster[32]). It is probable that the comparison of the transverse diameter of the heart with the prediction table of Ungerleider and Clark[72] gives a relatively accurate indication of the presence or absence of cardiac enlargement,[63] (Fig. 5) although these tables allow too high values for obese patients and are unsuitable in the presence of chest deformities, ascites or pregnancy. When the measured transverse diameter exceeds the predicted value by more than 10 per cent, the heart is probably enlarged; when it exceeds the predicted value by more than 15 per cent the heart is almost always enlarged.[71]

The Long and Broad Diameters. Other measurements are employed to determine enlargement of individual portions of the heart. The *long diameter* (or oblique diameter) of the heart (L) is the distance from the cardiac apex on the left to the junction of the right atrium with the superior vena cava or ascending aorta on the right. The average value of this dimension in the adult male is between 12 and 15 cm. Normally the long diameter is about 1.5 cm. or 10 per cent greater than the transverse diameter. It is increased chiefly by enlargement of the left ventricle.

The *broad diameter of the heart* (B) is the sum of the perpendicular (BR) from the point of junction of the right atrium with the diaphragm to the long diameter, and the perpendicular (BL) from the point of junction of the left ventricle with the pulmonary arc to the long diameter. The length of the broad diameter ranges between 8 and 11 cm. in the adult male. The broad diameter ranges between 65 and 85 per cent (average, 75 per cent) of the long diameter. If the broad diameter exceeds 85 per cent of the length of the long diameter, there is usually definite enlargement of the right ventricle. Based on the premise that the projected cardiac area conforms to an ellipse, the area is calculated as area $= \frac{3}{4}\pi \times L \times B$. If the calculated area exceeds by more than 10 per cent the predicted area as determined for normals of the given height and weight, cardiac enlargement is assumed.

The Depth, Volume and Surface Area. Measurement of the depth of the cardiac shadow, i. e., the longest anteroposterior dimension of the cardiac silhouette as seen in a lateral view, may reveal cardiac enlargement when other dimensions are normal. The depth of the heart averages between 9 and 10 cm. and is usually 60 to 85 per cent of the length of the transverse diameter.

The *volume of the heart* may be most accurately determined by the actual volumetric reconstruction of the heart as a plastic model whose volume is equal

to the amount of water it displaces when immersed. The construction of such models has been described by Lysholm,[45] Schatzki,[60] and by Palmieri.[53] The volume of the heart has been determined from measurements of the area in the anteroposterior view and the depth in the lateral view. Formulae for its calculation, suggested by Rohrer,[59] by Kahlstorf[36] and by Jonsell,[35] are based on the fact that the form of the heart is somewhat between that of an ellipsoid and a paraboloid. The volume equals length $\times$ width $\times$ depth $\times$ 0.63, the latter being a constant used because the heart resembles the figures mentioned rather than a regular three dimensional solid. Calculated thus, the average volume of the heart ranges between 650 and 700 cc. for the male, and between 500 and 550 cc. for the female. In general these calculations of cardiac volume have not proved of practical value in clinical practice.

The *area of the frontal cardiac silhouette* in relation to standards based on weight and height has been recommended as a criterion of cardiac size. To calculate this area Ungerleider and Gubner[73] used the formula area $= \frac{3}{4}\pi \times$ long $\times$ broad diameters and found the calculated values showed a mean deviation of less than 3 per cent from the actual area as measured by planimetry. They prepared a nomogram for direct reading, without calculation, of the frontal area when the broad and long diameters are known, as well as for the prediction of the normal area from weight and height (Fig. 5). The heart is considered enlarged if its frontal surface area exceeds predicted values by more than 10 per cent.

Factors Modifying the Normal Cardiac Silhouette. In sthenic individuals with a short, broad, rounded chest, the cardiac shadow tends to be short, wide and situated transversely, and the apex appears to be displaced to the left. Similar transverse positions suggesting left ventricular enlargement may be due to a high diaphragm, e. g., in deep expiration, with hepatic enlargement and ascites, during pregnancy and in obese subjects with meteorism. Scoliosis, even the slight scoliosis commonly seen in children, produces an apparent enlargement of the cardiac shadow because most of the heart lies to the left of the spine.[54] A similar effect is produced by funnel chest (p. 902).

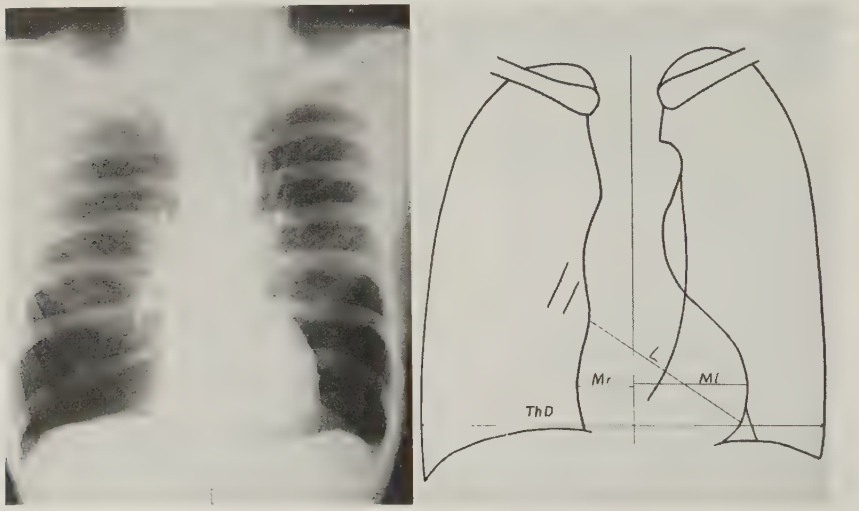
In asthenic individuals with a long flat narrow chest, the cardiac silhouette is long and narrow and its contours are only slightly convex. In its extreme form this type of heart is pear-shaped, centrally located, and is termed the cor pendulum or drop heart. A vertical cardiac shadow tends to occur during deep inspiration, in the erect as compared with the recumbent position, and in the presence of pulmonary emphysema.

Enlargement of the Individual Chambers

Cardiac enlargement may involve the entire heart, as in various toxic, infectious, and metabolic diseases, severe anemias, and certain forms of combined left- and right-sided heart failure. But in some of the most frequent and most important forms of cardiac disease, especially in their less advanced stages, cardiac enlargement is confined to a single chamber or to two chambers. These localized forms of enlargement are characteristic of certain diseases and are, therefore, of great diagnostic value. Kirch[39] showed that enlargement may be confined not only to a single chamber but even to a special portion of that chamber. The ventricles may be divided anatomically and physiologically into inflow and outflow tracts, the inflow tract being the posterior segment of the ventricle between the atrial ventricular ostium and the apex, and the outflow

tract being the anterior segment between the apex and the semilunar valve. This distinction has significant roentgenologic applications. It is important to note that enlargement of the ventricles begins in the outflow tract, first near the arterial ostium and then toward the apex, so that elongation of the chamber occurs. Only later, when the inflow tract becomes enlarged, is widening of the chamber seen roentgenologically. Thus, dilatation of a chamber may produce either elongation or widening. Since it is more difficult to recognize the former roentgenologically, the earliest stages of cardiac enlargement may be overlooked.

Left Ventricle. Early enlargement of the left ventricle begins in the outflow tract, involving the anterior wall and septum near the aorta. Since this region is not part of the cardiac border in the dorsoventral silhouette, it is not easily noted roentgenoscopically. Moderate left ventricular hypertrophy with minimal



A B

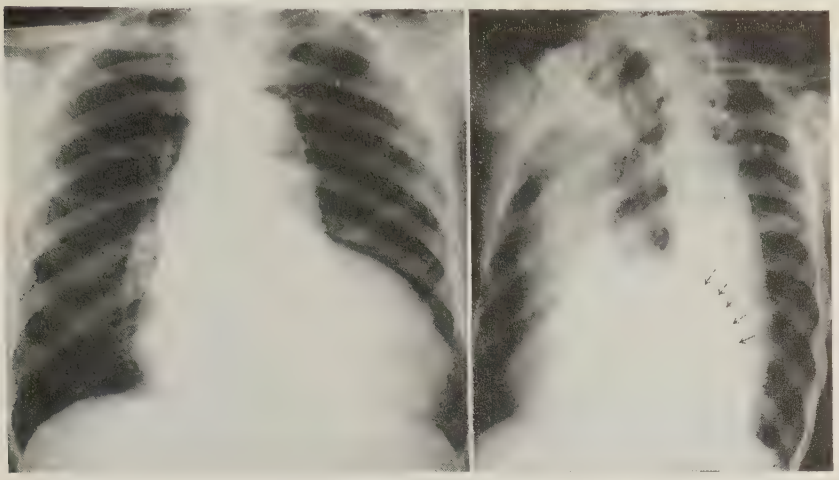
Fig. 6. *A*, Left ventricular hypertrophy in essential hypertension. Increased convexity of left ventricular contour. No increase in transverse or long diameters or in cardiothoracic ratio. So-called "concentric hypertrophy."

B, Sketch of *A* showing measurements. Ml = 7.8 cm.; Mr = 3.8 cm.; TD = 11.6 cm.; ThD = 27.6 cm.; L = 12.6 cm.

dilatation (so-called concentric hypertrophy), as seen in essential hypertension, may be characterized by moderate rounding of the left lower contour without significant alteration in cardiac diameters (Fig. 6). An early evidence of left ventricular enlargement is the elevation and elongation of the lower left cardiac contour with corresponding shortening of the left middle contour. With further elongation of the outflow tract, the left ventricular border is lower and more closely in contact with the diaphragmatic shadow. Later, when the inflow tract also becomes enlarged, the apex of the left ventricle becomes broad, rounded, and displaced to the left, so that the transverse diameter may also be increased (Fig. 7*A*). Although the transverse diameter may be increased with left ventricular enlargement, there is usually a greater increase in the long diameter.

Since the principal expansion of the left ventricle is dorsad, enlargement of this chamber is best seen in the left anterior oblique position (Fig. 7*B*). It pro-

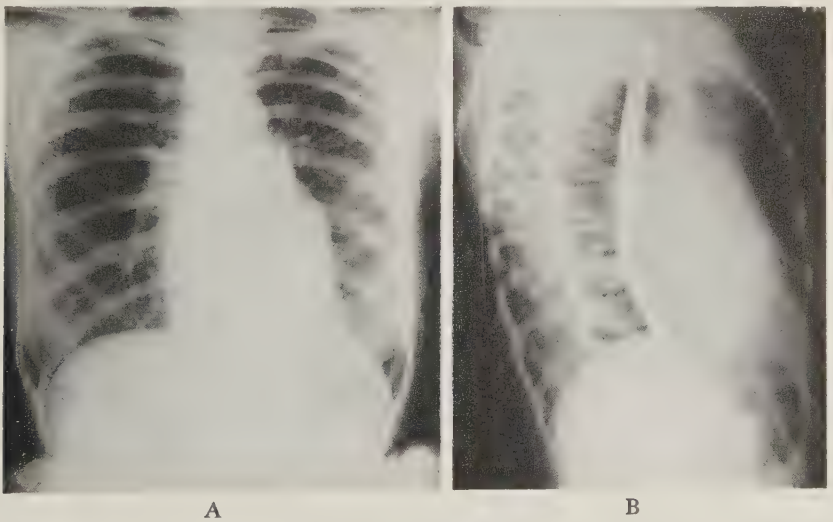
duces a bulge in the lower posterior contour, obliterating the retrocardiac space and overlapping the spine.



A B

Fig. 7. *A*, Left ventricular enlargement in advanced aortic insufficiency. Elongation and elevation of left ventricular contour, with increased rounding and displacement to the left.

B, Same case. Left oblique view. Posterior bulging of left ventricular contour (arrows). Obliteration of retrocardiac space and encroachment on spine.



A B

Fig. 8. *A*, Left atrial enlargement in mitral stenosis. Prominent left middle salient due to enlarged left atrium below and elevated pulmonary artery above.

B, Same case. Right oblique view. Posterior bulging of enlarged left atrium with diminution of retrocardiac space, posterior displacement and compression of barium-filled esophagus.

It is important to distinguish left ventricular enlargement from displacement of the cardiac shadow to the left. In normal individuals, apparent enlargement of the left ventricle is usually due to a high diaphragm. It should also be empha-

sized that displacement of the left lower cardiac contour to the left may be caused by enlargement of the right ventricle (see below).

Left Atrium. When the left atrium enlarges, it does so chiefly posteriorly and to the right. However, in the posteroanterior view the enlarged left atrium, especially its appendage, may cause a straightening of the left border or a prominence of the middle salient (Fig. 8*A*). To a variable degree this effect is due

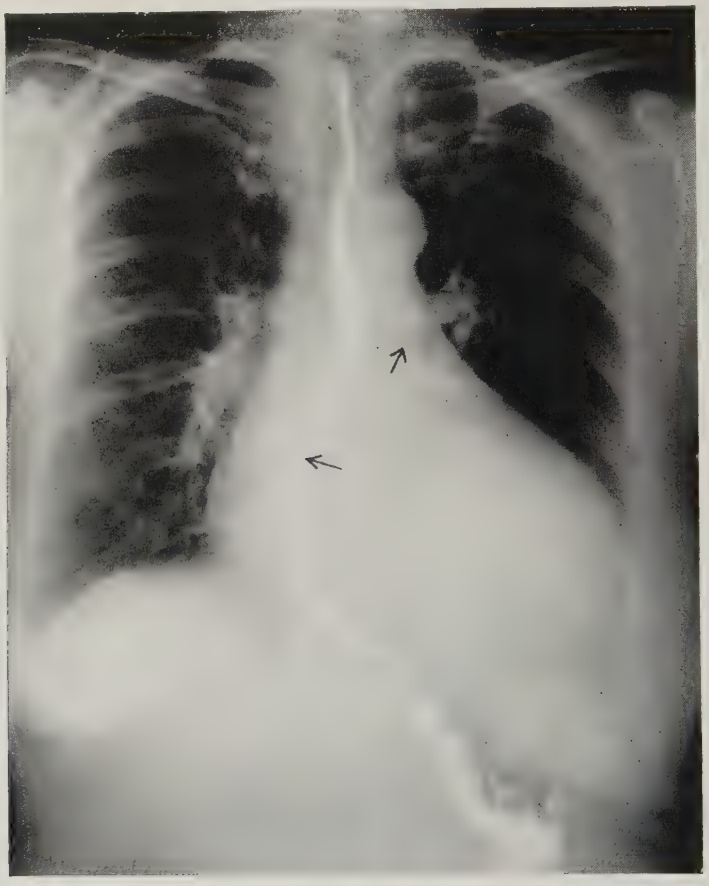


Fig. 9. Left atrial enlargement in advanced mitral stenosis and heart failure. Compression of barium-filled esophagus and displacement to the right (lower arrow). Left bronchus (upper arrow) elevated almost to horizontal position by dilated left atrium.

also to associated elevation and dilatation of the pulmonary artery. The posterior enlargement is best observed in the right anterior oblique position. (Fig. 8*B*). In this view, the normally clear retrocardiac space is encroached on by the large left atrium or obliterated, except for a small triangular area just above the diaphragm. At the same time, the left main bronchus may be elevated and flattened and the angle of bifurcation of the trachea increased.[38, 20, 66] In the left oblique view, obliteration of the normal clear area between the upper border of the left atrium and the left main bronchus precedes elevation or obstruction of the latter.

Enlargement of the left atrium is more clearly indicated by compression of

the esophagus.[58, 18] In the anteroposterior view, the barium-outlined esophagus is abruptly and conspicuously displaced to the right and the stream is partially obstructed (Fig. 9). In the right anterior oblique view, the normal curve of the left atrium, as outlined by the barium-containing esophagus, is conspicuously deepened and displaced posteriorly (Fig. 8*B*).

If the left atrium is very enlarged, its outline in the dorsoventral view appears on the right border (Fig. 10). A double right cardiac contour may thus be

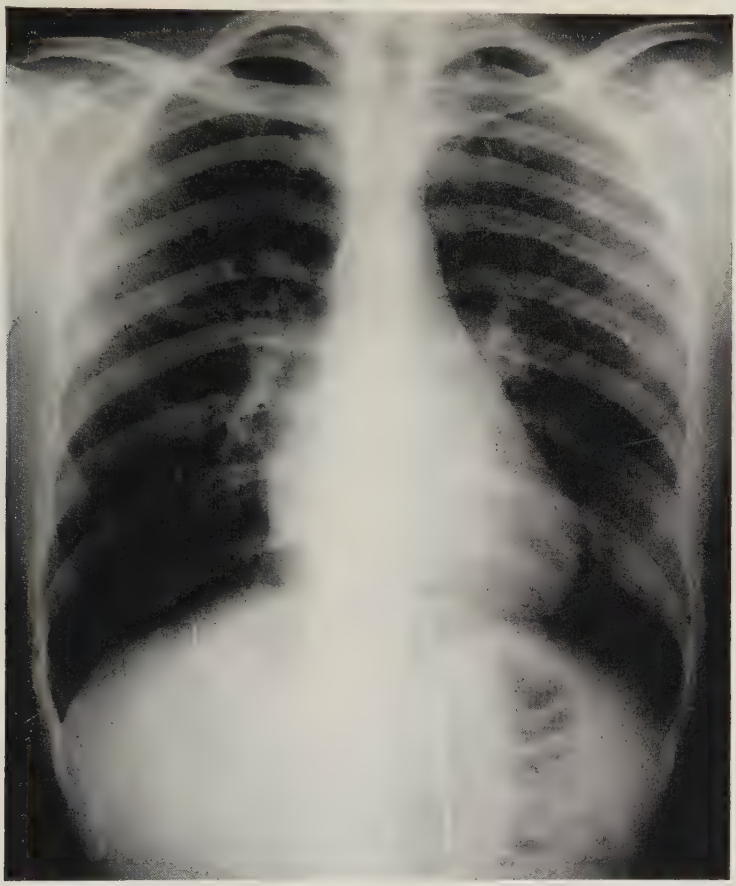


Fig. 10. Enlarged left atrium in mitral stenosis. Globular shadow of hypertrophied left atrium appears as distinct density within cardiac shadow. Extends on right beyond right atrial border. On upper left it elevates left bronchus.

formed, the upper consisting of the left atrium, and the lower of the right atrium. With extreme enlargement of the left atrium, especially in the so-called "giant left auricle," the above abnormalities are exaggerated and the entire right cardiac border is formed by that chamber, which may extend far into the right pulmonary field. It may appear also on the left border as a conspicuous segment below the pulmonary artery. With pronounced enlargement, the density of the left atrium also increases and its shadow can actually be distinguished within the cardiac shadow (Fig. 10).

Right Ventricle. Enlargement is difficult to diagnose in its early stages

on the basis of conventional roentgenograms, for the enlargement is usually anterior and does not cause the chamber to reach the cardiac borders. Enlargement of the right ventricle is then recognized by its indirect effects, namely, elevation and rotation of the pulmonary artery, which fills out the waist of the cardiac silhouette and results in straightening of the left border or convex prominence of the pulmonary salient (Fig. 11). Furthermore the conditions responsible for right ventricular enlargement often cause pulmonary artery dilatation which also accents the left middle cardiac salient. With extreme enlargement the pulmonary conus rotates clockwise on the long axis of the heart and may participate in the left pulmonary salient. Since straightening of the left border and prominence of the pulmonary salient occur most often with mitral stenosis, this distinctive configuration has been termed "mitralization"

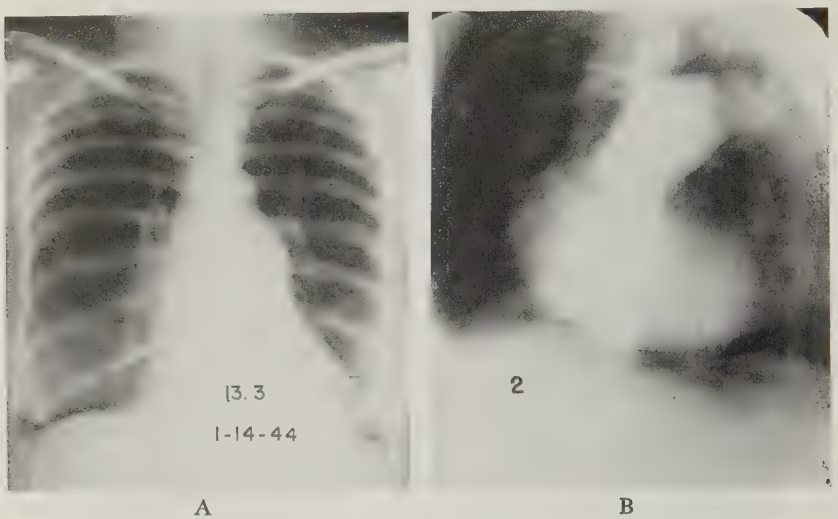


Fig. 11. *A*, Enlargement of right ventricle. Chronic cor pulmonale. Prominence and elongation of left middle (pulmonary) segment due to dilated elongated pulmonary artery. Right ventricle does not reach cardiac borders in this view. In right oblique view enlarged right ventricle bulged anteriorly obliterating retrosternal space.

B, Angiocardiogram, same case. Left oblique view. Opacification of pulmonary artery with diodrast shows pronounced dilatation of that vessel.

of the heart. But in mitral stenosis it is the enlarged left atrium and not the dilated pulmonary artery which forms the major portion of the prominent middle salient.

Enlargement of the outflow tract of the right ventricle may be observed in the right anterior oblique as an anterior projection of the lower contour toward the sternum, and in lateral views by obliteration of the retrosternal space.

When the right ventricle is conspicuously enlarged (in its inflow as well as outflow tracts), it may rotate sufficiently to form most or all of the left cardiac border, including the apex of the heart. The original apex is elevated by the enlarged right ventricle with a resultant characteristic rounding of the lower left contour, as seen in the tetralogy of Fallot (coeur en sabot, p. 653). The enlarged right ventricle may also displace the right atrium to the right. Both of these factors tend to increase significantly the transverse diameter of the heart.

Enlargement of the inflow tract is best seen in the left anterior oblique posi-

tion. The diaphragmatic surface formed by the right ventricle is increased, the notch between it and the left ventricle being displaced posteriorly toward the spine.[51] However doubt has been cast on this localization of the interventricular groove by angiocardiographic studies.[67] Anteriorly, the lower cardiac border, representing the right ventricle, bulges prominently and may form a conspicuous angulation where it joins the contour of the right atrium above it.



Fig. 12. Generalized chamber enlargement. Mitral, aortic and tricuspid valvular disease. Right atrium enlarged to right and upward. Left atrium extends to both borders.

Angiocardiography discloses right ventricular hypertrophy by a change in the curvature of the interventricular septum. Normally the septum is convex to the right; with right ventricular hypertrophy unaccompanied by left ventricular hypertrophy the septum becomes straightened and later convex to the left.

Right Atrium. When the right atrium enlarges, it expands chiefly to the right, but also upwards and posteriorly. Roentgenoscopically, its enlargement is denoted in the anteroposterior view by outward displacement of the right lower cardiac contour. Displacement to the right may, however, be caused also by enlargement of the right ventricle occasionally, and by that of the left ventricle rarely. When the displacement reaches the right midclavicular line, the right atrium is definitely enlarged but this is usually part of a generalized cardiac

enlargement, or is due to combined mitral, aortic and tricuspid valvular disease (Fig. 12), or congenital atrial septal defect.

In the right anterior oblique position, the enlarged right atrium encroaches on or obliterates the lowermost portion of the retrocardiac space but it does not displace the esophagus.

In the left anterior oblique position, the large right atrium causes a bulge in the upper anterior cardiac segment. Enlargement of the right atrium may be simulated not only by enlargement of the ventricles, but rarely also by an aneurysm of the ascending aorta reaching down toward the diaphragm, by an arteriosclerotic dilated descending aorta, and by para-esophageal hernia.

ELECTROCARDIOGRAPHIC SIGNS OF CARDIAC ENLARGEMENT

The electrocardiogram may suggest or corroborate the presence of cardiac enlargement. The clinical and roentgenologic findings should be considered in making a diagnosis of cardiac enlargement on the basis of the electrocardiogram. The electrocardiogram does not reveal uniform, generalized enlargement of the heart but may be characteristically altered by disproportionate enlargement of one of the chambers.

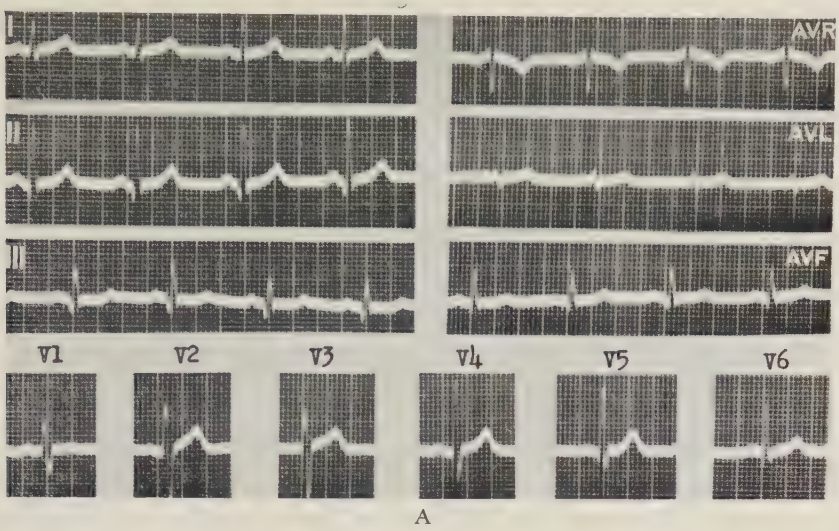
A number of factors which have been cited above as altering the size and form of the cardiac silhouette likewise alter the form of the electrocardiogram. Just as we must distinguish roentgenograms of cardiac displacement or rotation from somewhat similar ones of cardiac enlargement, so we must distinguish the electrocardiographic changes due to cardiac enlargement from those caused by the position or rotation of the heart within the chest.

Deviation of the Electrical Axis

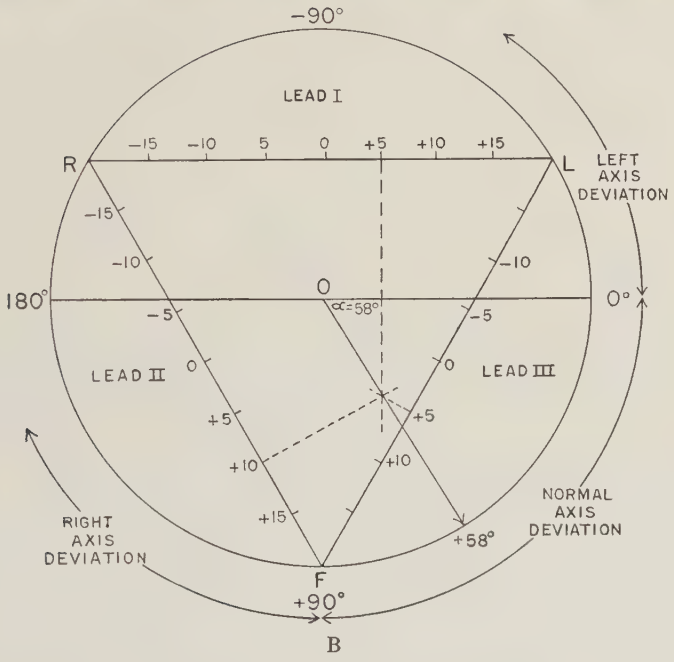
The Mean Electrical Axis. The QRS complex and other waves of the electrocardiogram are the graphic delineations, in a frontal plane, of the electromotive potentials developed in the heart during its depolarization and repolarization (Fig. 13*A*). The mean electrical axis is the mean representation of the magnitude and the average direction of these varied potentials. The electrical axis is a vector because it possesses magnitude and direction. The vector of the electromotive force at any given moment is known as the instantaneous electrical axis. The mean electrical axis of the QRS is the sum of the instantaneous electrical axes of the QRS; the mean electrical axis of the T may be similarly considered. The electrical axis of the heart is a vector in three-dimensional space and usually is directed downward, backward and to the left. Since it is not parallel to the frontal plane, its effect on the limb leads represents only its projection in that frontal plane.

Determination of the Mean Electrical Axis. Various methods have been devised to determine the mean electrical axis and other vectors of the electrical forces evolved during depolarization and repolarization of the heart.

1. *Einthoven's Triangle.* Einthoven proposed that the right and left forearms and left leg to which the leads of the electrocardiograph are attached may be considered as the vertices of an approximate equilateral triangle with its base above and its apex below (Fig. 13*B*). The sides of the triangle may represent the flow of current in the three leads. With this concept as a premise, it can be shown that the algebraic sum of any complex in lead I and lead III, recorded simultaneously, is equal to that complex in lead II, at the same instant, i. e., $R_2 = R_1 + R_3$; $P_2 = P_1 + P_3$, etc.[17] Although the equilateral triangle theory



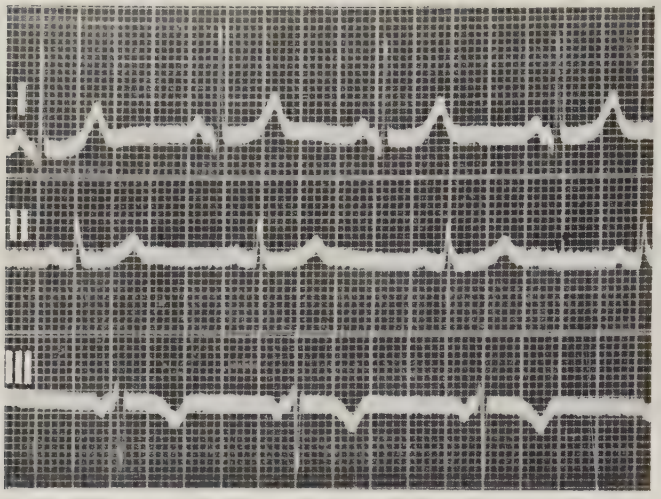
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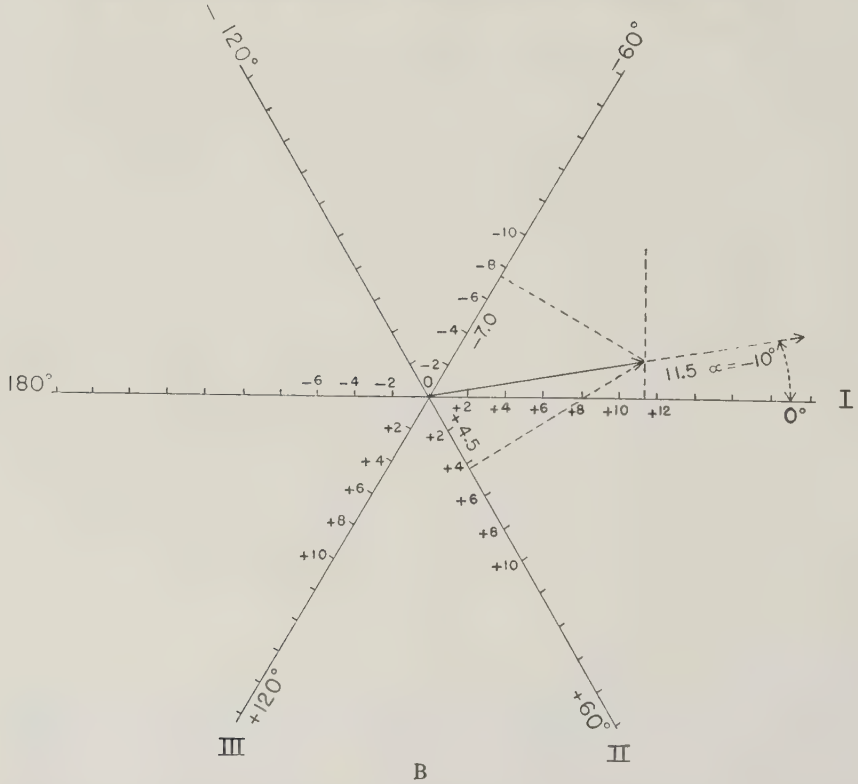
B

Fig. 13. *A*, Normal electrocardiogram. Standard leads on left. Augmented unipolar limb leads on right. Unipolar precordial leads below. R taller than S in V_1. S increases to V_3 and then diminishes. Transition point between V_3 and V_4. Q absent in V_1, diminutive in V_5 and V_6.

B, Einthoven's triangle with representation of normal electrical axis of QRS in electrocardiogram in Fig. 13*A*. Angle of deviation 58°. R_1 (6) — S_1 (1.0) = 5. R_2 (12) — Q_2 (2) = 10. R_3 (7) — Q_3 (2) = 5. It is assumed the leads were taken simultaneouslv.



A



B

Fig. 14. *A*, Left axis deviation due to horizontal position of the heart. Tall R_1, small R_3, deep S_3, P_3 and T_3 inverted.

B, Triaxial reference system with representation of electrical axis of QRS in Fig. 14*A*. R_1 (13) − Q_1 (1.5) = 11.5. R_2 = 4.5. R_3 (1.0) − S_3 (8) = −7. It is assumed that simultaneous leads were taken. The angle of deviation from the horizontal (−10°) denotes axis deviation to the left of normal.

has been criticized,[81] it has proved extremely valuable in our understanding of the electrocardiogram and is essentially correct for most cases.

The mean electrical axis may be determined diagrammatically from the Einthoven triangle.[11] A circle is circumscribed about it and its circumference marked off in degrees with 0° at the three o'clock point and ±180° on the nine o'clock point of a transverse diameter and minus 90° at the upper and plus 90° at the lower end of a vertical diameter. The center of the triangle (and circle) is the starting point of the vector line representing the mean electrical axis. The angle alpha made by the electrical axis with the transverse diameter is called the *angle of deviation*. The axis is determined from any two leads, but it is best to use those with the most distinct R or S waves.

The algebraic sum of R_1 and S_1 in millimeters is plotted on the line of lead I, positive values being marked off from the midpoint of the line toward the 0° end and negative values toward the 180° end.

Similarly the algebraic sum of R_3 and S_3 (or R_3, Q_3 and S_3) is plotted on the line representing lead III, positive values going below and negative values above the center of the line. From these plotted points perpendiculars are erected on the lead lines and extended until they meet. A line drawn from the center of the triangle to this meeting point is the vector of the mean electrical axis. If this line is extended to the circumference the *axis deviation* from the horizontal may be read off the circumference in degrees. The normal mean electrical axis lies between 0 degrees and +90 degrees. Left axis deviation indicates an angle between 0 and minus 60°, while right axis deviation indicates an angle between 90° and 150° on the above diagram.

2. *The Triaxial Reference System.* This method, based on the Einthoven triangle, may also be used to determine the mean electrical axis[7] (Fig. 14). A circle is drawn with a horizontal diameter and two oblique diameters passing through the center at a 60° angle to each other. The three o'clock end of the horizontal line, which represents lead I, is labelled 0°, the nine o'clock end ±180°; the oblique diameter running from above downward, and toward the 0° side represents lead II and is labelled −120° above and +60° below; the oblique diameter running from above downward and toward the 180° side represents lead III and is labelled −60° above and +120° below.

As directed above in the use of the Einthoven triangle, the values of $R_1 + S_1$ and of $R_3 + S_3$ are plotted on two of the lead lines beginning at the center of the system and going to the 0° point or downward for positive values and upward or toward the 180° point for negative values. Perpendiculars to the lead lines are dropped through the plotted points until they meet. The mean electrical axis is represented by the line drawn from the center to this point of intersection. Extension of this line to the circumference will give the angle of deviation of the electrical axis.

The chart of Dieuaide[14] is also used to determine the mean electrical axis and is based on the same principles.

The Monocardiogram or Vectorcardiogram. By recording several instantaneous electrical axes from simultaneous points on two limb leads according to the above methods a series of vectors is obtained. If the terminus or heads of these vectors are joined, the resulting figure forms a loop. This is known as the monocardiogram[47] or vectorcardiogram[61, 76] (Fig. 15). A method of constructing vectorcardiograms has been described by Mann[47] and more recently by Howard.[34] The single polar curve representing these continuous electrical

axes of cardiac depolarization can also be obtained directly by a cathode ray oscillograph, or by a galvanometer capable of responding simultaneously to three separate electrical currents which have been greatly amplified after coming from the three leads. The single curve or loop thus obtained permits the recognition of left or right deviation of the electrical axis by direct inspection of its direction and the location of its long axis. Normally the vector of the QRS rotates in a clockwise direction and its long axis is situated between 0° and 90° in the triaxial reference system.[21]

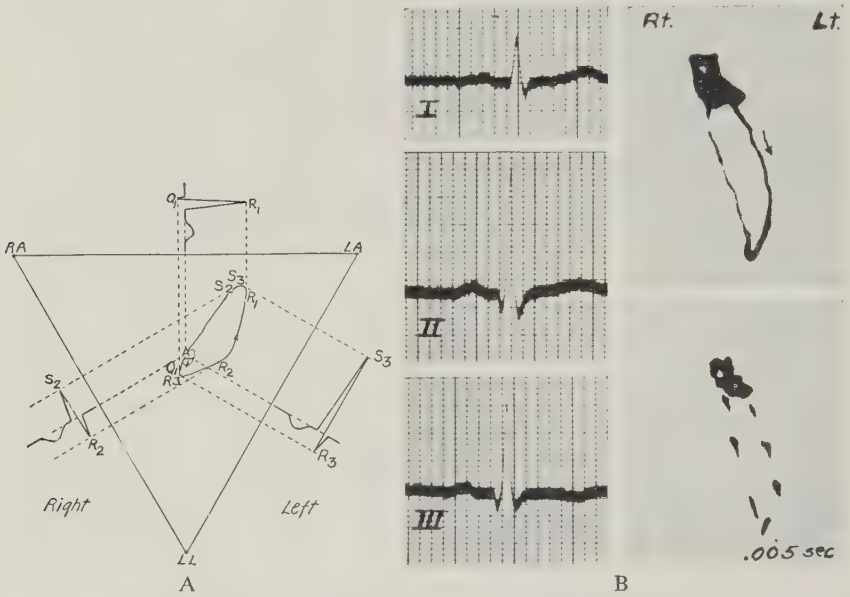


Fig. 15. Vectorcardiogram. *A*, Relations between vectorcardiogram and standard limb leads. Former is loop formed by connecting terminus of vectors representing electrical axis from moment to moment.

B, Electrocardiogram of a normal subject and corresponding vectorcardiogram recorded with aid of cathode ray oscillograph. Large loop is vectorcardiogram of QRS; black area is that of P and T. Loop is clockwise (negative) and its major axis represents an angle of deviation of about 75°. (Wilson and Johnson, American Heart Journal, Vol. 16.)

Ventricular Gradient. This is a vector representation on a frontal plane of the duration of the net differences of electrical activity in different parts of the myocardium during depolarization and repolarization.[79] The ventricular gradient, represented as $\hat{G}$, can be determined from the areas of the QRS and T waves. The *areas* of the QRS and T waves in leads I and III are measured in microvolt seconds, each square of the electrocardiograph paper representing 0.04 microvolt second or 1 unit. These areas denote respectively the mean force of the depolarization process and of the repolarization process, and may be represented as vectors $\hat{A}_{QRS}$ and $\hat{A}_T$. Since the heart is three-dimensional, these vectors are actually spatial vectors, but in our discussion we are concerned only with their projection on a plane surface.

The area $QRS_2 =$ area $QRS_1 +$ area QRS_3 in simultaneous curves just as we have seen by Einthoven's theory $R_2 = R_1 + R_3$. If the areas of QRS of

any two leads are plotted as microvolt seconds on the sides of the Einthoven triangle or in the triaxial reference system, a vector is obtained, $\hat{A}_{QRS}$, which represents the electrical axis during the *whole period* of the QRS just as we previously obtained the electrical axis at the point of maximal amplitude. Similarly by plotting the areas of the T wave in two leads a vector $\hat{A}_T$ is obtained for the electrical axis during the entire period of T. The ventricular gradient $\hat{G}$ is obtained on the same triaxial reference diagram, as the resultant of $\hat{A}_{QRS}$ and $\hat{A}_T$ by the law of the parallelogram of vector forces. Further discussion of this subject is beyond the scope of this book. It is mentioned here because of its relation to rotation of the heart about its various axes[1] and the information it contributes to our understanding of axis deviation.[2]

The Recognition of Axis Deviation. *1. Mean Electrical Axis.* One means of discovering deviation of the electrical axis from the normal or usual is to determine the vector representing the mean electrical axis of the heart by the Einthoven triangle or triaxial reference system, and note the angle of deviation from the horizontal. Normally the electrical axis of the heart is directed downward and to the subject's left, making an angle of 0° to 90° with the horizontal. When the electrical axis is rotated counterclockwise or to the left, the angle of deviation becomes negative; when the electrical axis is rotated clockwise or to the right, the angle of deviation becomes more than 90°.

2. Vectorcardiogram. Axis deviation may also be recognized from the vectorcardiogram. Left axis deviation is disclosed by a negative or counterclockwise loop with its long axis making an angle between 0° and minus 90° with the horizontal. Right axis deviation is disclosed by a positive or clockwise loop with its long axis making an angle of 90° to 150° with the horizontal.

3. Ventricular Gradient. The ventricular gradient $\hat{G}$ and the vectors $\hat{A}_{QRS}$ and $\hat{A}_T$ are likewise modified by deviation of the electrical axis. In left or counterclockwise deviation the axis of QRS, $\hat{A}_{QRS}$, swings further to the left of the anatomical longitudinal axis than the ventricular gradient $\hat{G}$; in right or clockwise deviation, $\hat{A}_{QRS}$ swings further to the right of the anatomical axis than does $\hat{G}$.

4. Direct Inspection of Q, R and S. Normally the electrical axis has been noted to be directed downward and to the subject's left at any angle of 0° to 90° with the horizontal. As the heart is rotated to the left or counterclockwise on its anteroposterior axis, its mean electrical axis becomes more nearly parallel to the lead I line in the triaxial reference system and more nearly perpendicular to lead III. Therefore the positive voltage in lead I, represented by R_1, becomes higher and the voltage in lead III represented by R_3 becomes lower. When the rotation of the electrical axis to the left (or counterclockwise) is so great that it is directed to the subject's left and upward, the angle with the horizontal becomes negative and the maximal voltage in lead III diminishes below 0° and becomes reversed. This is indicated by an inverted major deflection or a deep S_3, while R_1 remains tall. Electrocardiographic curves with a tall R wave in lead I (taller than R_2) and a deep S wave in lead III are said to show *left axis deviation* (Fig. 14*A*). A Q_1 is often present but no Q_3. T_3 may be inverted and occasionally P_3.

As the electrical axis of the heart is shifted to the right or clockwise, it be-

comes more nearly parallel to lead III and more nearly perpendicular to lead I. The maximal voltage in lead III and therefore the R wave in that lead become higher while the voltage and R wave in lead I become lower. As the electrical axis comes to be directed downward and to the subject's right (instead of to the left as is normal), the angle with the horizontal exceeds 90 degrees, the voltage diminishes below 0 in lead I and becomes negative and the main electrocardiographic deflection is inverted. Thus there is a deep S_1 while R_3 is tall (Fig. 17).

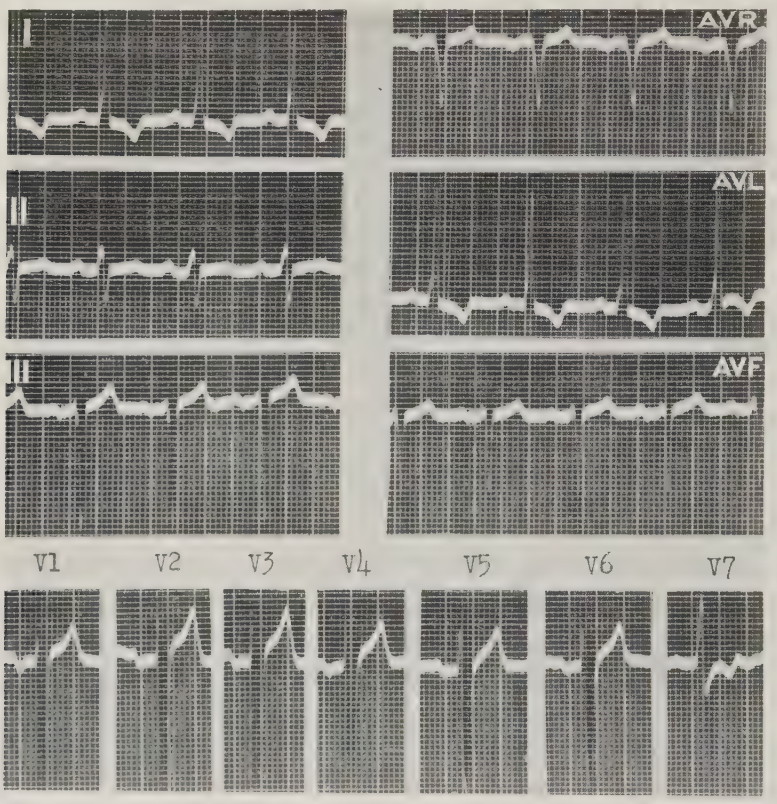


Fig. 16. Enlargement of the left ventricle (left ventricular strain). Tall R_1, diminutive R_3 with deep S_3. ST_1 slightly depressed and T_1 inverted in standard leads. Small R in V_1 and deep S in right precordial leads. Tall R, delayed peak of R and inverted T in V_7 over left ventricle. Counterclockwise rotation (horizontal heart) shown in unipolar limb leads by negative major deflection in left leg lead (aVF) and high R in left arm lead (aVL).

Electrocardiograms with a tall R_3 (taller than R_2) and a deep S_1 are described as showing *right axis deviation*. There may be a Q_3 but no Q_1. T_1 and P_1 may be of low voltage or inverted.

The simplest and most practical way of determining the presence of left or right axis deviation is by inspection. The degree of axis deviation can be roughly evaluated by noting the height or depth of the R and S waves. Thus, the taller R_1 and the deeper S_3 are, the greater the degree of left axis deviation, and the taller R_3 and the deeper S_1 are, the greater the degree of right axis deviation.

5. Unipolar Limb Leads. Unipolar limb leads are obtained by attaching the

exploring electrode to the limb to be examined, the remote electrode being attached by a V connection to the other two extremities.[22] If the heart is rotated to the left or counterclockwise the main deflection in the unipolar lead from the left leg (V_F) is downward (Fig. 16), since this lead faces the right ventricle and great vessels and therefore the zone of negativity behind the advancing wave of the cardiac impulse. If the heart is rotated to the right or clockwise the main deflection in V_F is more strongly positive than usual for it faces more of the left ventricle than normally, while the main deflection in the left arm unipolar lead (V_L) faces the right ventricle and will become negative[78, 23] (Fig. 17). The presence and depth of downward or S waves in V_F and V_L indicate positional changes in the heart responsible for left and right axis deviation. Furthermore in cases of *left axis deviation* or *horizontal heart,* V_L tends to resemble the unipolar precordial leads V_5 and V_6, while V_F resembles V_1 or

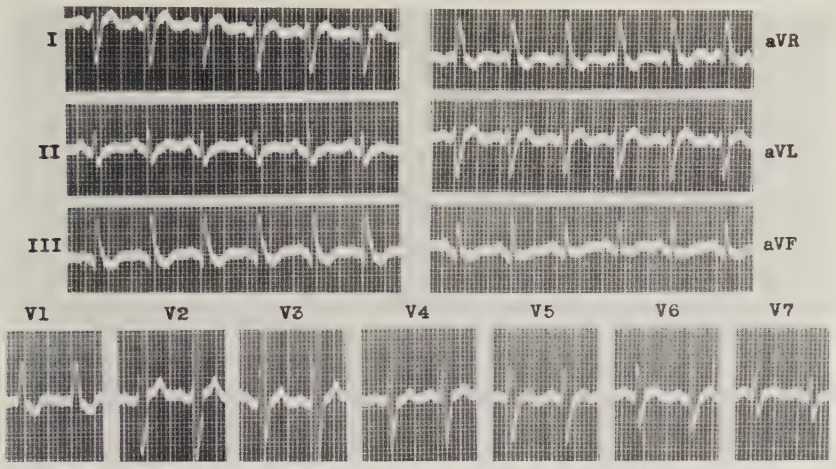


Fig. 17. Enlargement of right ventricle (right ventricular strain). R_3 taller than R_1 and deep S_1 in standard leads. R tall and larger than S, and T inverted in V_1. Unipolar limb leads show upright major deflection in aVR resembling aVF with inverted major deflection in aVL, indicating vertical position or clockwise rotation of the heart.

V_2. In cases of *right axis deviation* or *vertical heart* V_L tends to resemble V_1 and V_2 while V_F resembles V_5 and V_6.[77]

Axis Deviation Due to Positional Change or Cardiac Enlargement. The electrocardiographic changes associated with deviation of the electrical axis to the left or right have sometimes been described as denoting left ventricular or right ventricular preponderance, i. e., they were presumed to indicate disproportionate hypertrophy or enlargement of the left or right ventricle.[44] Indeed, left and right ventricular enlargement are common causes of pronounced left or right axis deviation, but the patterns of the latter are often produced in the absence of cardiac enlargement[10, 30, 48] and in fact right axis deviation may occasionally be encountered in a heart with left ventricular enlargement.[77]

The electrocardiographic pattern of left axis deviation is also observed in the constitutional sthenic person with a transversely situated heart, in obese subjects with a high diaphragm, or in those with a high diaphragm due to ascites or pregnancy. A deep expiration accentuates the left axis deviation.

The electrocardiographic pattern of right axis deviation is observed in

asthenic individuals with a centrally situated vertical or drop heart and in those with pulmonary emphysema and a low diaphragm. It is accentuated by a deep inspiration and the upright position. Right axis deviation is present at birth. It may be produced by lateral rotation of the body to the left.

In addition to the effects of position of the heart and ventricular hypertrophy on axis deviation, bundle branch block may also modify the apparent electrical axis by modifying the development of potential variations in the two ventricles.

The Electrocardiogram in Enlargement of the Left Ventricle (Left Ventricular Strain)

The following electrocardiographic changes are usually observed in conditions associated with predominant enlargement of the left ventricle: (hypertensive heart, aortic valvular disease, congenital subaortic atresia or tricuspid atresia).

(1) *Left axis deviation:* S_3 is of greater amplitude than R_3; R_1 is higher than R_2 or R_3. This in itself suggests disproportionate left ventricular enlargement if the deviation to the left is pronounced (mean electrical axis between minus 20 and minus 60 or as indicated by deep S_2) but there are many exceptions in which the axis deviation is due entirely to a transverse position of the heart. However, pronounced left axis deviation may be more significant of left ventricular hypertrophy if clinical and roentgenologic study excludes elevation of the diaphragm, pregnancy, obesity or other causes of a transverse position of the heart. Occasionally there may be normal or even right axis deviation in the standard limb leads despite left ventricular enlargement.[4, 65a] The latter may then be discovered from the precordial leads while the position of the heart will be revealed by unipolar limb leads.

(2) *R_1 or S_3 may have an abnormally high voltage* (above 17 mm.). This has only the significance of a *pronounced* left axis deviation.

(3) *ST_1 is depressed and ST_3* may be *slightly* elevated. T_1 is *very low or inverted and T_2 may also be low or inverted.* In cases of left axis deviation due to rotation of the heart there may be inversion of the T wave in lead III but not in lead I.[27]

(4) The QRS interval may be prolonged to 0.10 or 0.11 second. This may be due to delay in passage of the electrical impulse from subendocardium to pericardium through the increased thickness of left ventricular muscle or to delay caused by elongation or functional depression of the left bundle branch.

(5) *Multiple, unipolar precordial leads provide the most reliable evidence of left ventricular hypertrophy.*

(a) The R wave is absent or minute in V_1, V_2 and V_3 and there is a deep S wave in these leads.

(b) The R wave over the enlarged left ventricle in V_5 or V_6 is of high voltage and there may also be a deep Q wave. R in V_5 exceeds 26 mm. and R in $V_5 + S$ in V_1 exceed 35 mm.

(c) The R wave occurs relatively late in the QRS interval (0.05 second or more) and the QRS interval may be slightly prolonged to 0.10 second or even 0.11 second.

(d) The transition point at which R becomes as high or higher than S shifts from about V_3 to V_4 or further to the left.

(e) The T waves are inverted in V_5 and V_6 and the ST segment is depressed. According to Wood and Selzer,[83] left axis deviation without

hypertrophy may cause inversion of T in V_1 and occasionally in V_2 but not in V_5.

The Electrocardiogram in Enlargement of the Right Ventricle (Right Ventricular Strain)

The following are the common electrocardiographic findings in conditions associated with predominant enlargement of the right ventricle (mitral valvular disease, cor pulmonale, most types of congenital heart disease, especially interatrial septal defect and pulmonic stenosis) (Fig. 17):

(1) *Right axis deviation:* S_1 is of greater amplitude than R_1; R_3 is higher than R_1 or R_2. This may suggest right ventricular enlargement if the right axis deviation is pronounced (deep S_2, mean electrical axis between $+100°$ and $+120°$). However these changes are often due to a vertical heart alone. If a vertical heart, a low diaphragm and pulmonary emphysema can be excluded roentgenologically, evidence of pronounced right axis deviation is strongly suggestive of right ventricular enlargement.

(2) R_3 and S_1 may have an abnormally high voltage (especially in congenital atrial septal defect or pulmonic stenosis). This finding increases the probability that right axis deviation is due to right ventricular enlargement.

(3) T_3 and T_2 are inverted and ST_2 and ST_3 are depressed. In association with evidence of right axis deviation this is often regarded as diagnostic of right ventricular enlargement.[6] But there are exceptions to this rule.[77, 23, 24, 50]

(4) *The precordial leads are most reliable for the diagnosis of right ventricular enlargement.* The following changes are usually observed:

(a) The R wave is high in V_1 and may be delayed (interval of 0.03 to 0.05 second); S is absent; Q is often present and T is inverted.

(b) The R deflections are small in V_5 and V_6 and there are deep S waves in these leads. Thus there is a reversal in the normal ratio of the amplitudes of R and S in V_1 and V_6.

The term ventricular enlargement, rather than hypertrophy, is used in the above electrocardiographic interpretations as it has been in the clinical and roentgenologic discussion. For the effects on the electrocardiogram may be due at least as much to dilatation or elongation of a chamber with consequent rotation of the heart or prolongation of conduction time as to the increase in muscle mass, i. e., hypertrophy. In fact studies based partly on endocardial potentials of the hypertrophied right ventricle indicate that the latter causes right axis deviation, not by itself but by changing the position of the heart in the thorax.[41]

The Electrocardiogram in Enlargement of the Atria

The P wave represents depolarization of the atria. Normally this wave is not more than 1.5 to 2.0 mm. high, and its duration is not more than 0.1 second in any lead.[19, 82] With enlargement of the atria the P waves may become notched, increased in amplitude and in duration. Widening of P may be due to dilatation of the atria with consequent prolongation of the depolarizing process or to disease within the wall. An abnormally high amplitude has been attributed to hypertrophy, while notching has been related either to irregularly distributed areas of disease or to unequal dilatation of the right and left atria. Atrial activity may be best disclosed by esophageal leads or by right parasternal chest

leads.[68a, 9a] Right atrial enlargement may be characterized by diphasic P waves with a prominent intrinsic deflection.

According to Berliner and Master,[9] notching of the P waves occurs in uncomplicated mitral stenosis, but broad P waves of very high amplitude are usually found when tricuspid disease is also associated. Tall, broad and deeply notched P waves, usually in leads I and II, have been described as mitral P waves and have been associated with mitral valvular disease[28, 75] (Fig. 18*A*). On the other hand, enlargement of the right atrium secondary to chronic pulmonary disease has been characterized by tall, sharply peaked P waves in leads II and III[37, 80, 64] (Fig. 18*B*). However, this type of pulmonary P wave

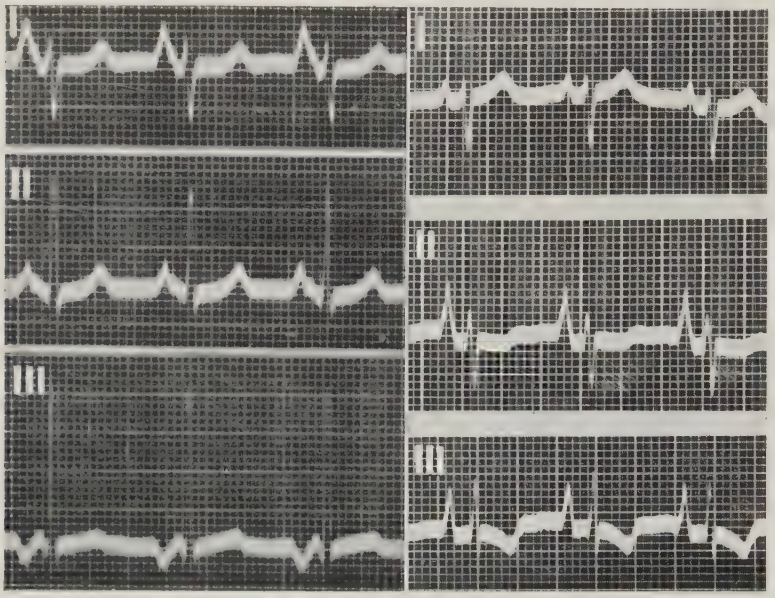


Fig. 18. *A,* (Left) atrial enlargement in mitral stenosis. P waves tall, notched and widened in leads I and II. Right ventricular strain.

B, (Right) atrial enlargement in chronic cor pulmonale secondary to asthma and obstructive emphysema. P waves tall and pointed (peaked) in leads II and III but not widened. Right ventricular strain or right axis deviation.

may occur in normal hearts due to a vertical position of the heart with forward displacement of the apex, perhaps related to an associated low diaphragm and pulmonary emphysema.[24]

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4

ETIOLOGY OF CHRONIC (CONGESTIVE) HEART FAILURE

Circulatory failure has been classified into the acute and chronic forms (Chapter 2). The acute form, which includes shock, syncope and sudden death, is discussed in Chapter 10. The present chapter and the succeeding five chapters are concerned with the chronic form of circulatory failure which is generally known as congestive heart failure.

This chapter presents the factors or mechanisms which render the heart incapable of maintaining an adequate cardiac output, or of maintaining it without the aid of extracardiac compensations. The mechanism by which this cardiac disability leads secondarily to the clinical manifestations of congestive heart failure is discussed in subsequent chapters (6 and 7). The etiology of congestive heart failure will be discussed under the following headings: (1) Fundamental Mechanism; (2) Precipitating Clinical Causes; (3) Underlying Causes.

THE FUNDAMENTAL MECHANISM OF CARDIAC FAILURE

When cardiac failure occurs shortly after a toxic, infectious disease such as diphtheria, we assume that sufficient muscle tissue has been destroyed or its contractility so greatly impaired by bacterial toxins that the heart is unable to maintain the circulation. It is incomprehensible, however, why cardiac failure so often develops in a patient whose valvular, hypertensive or arteriosclerotic heart disease has appeared entirely static and well compensated. Frequently we suspect a recurrent or intercurrent infection, a progressive diminution in the coronary blood supply, physical strain or some other so-called precipitating factor, but we are at a loss to understand exactly how this factor induced cardiac failure. Investigations to determine the mechanism of cardiac failure have been conducted along three lines: (1) The pathologic changes in the heart which has failed. (2) The relationship of cardiac hypertrophy to cardiac failure. (3) The chemical changes in the heart.

The Pathologic Basis of Cardiac Failure

Extent of Anatomic Alterations in Heart with Failure. It has long been customary to attribute cardiac failure to anatomic changes in the heart. Yet it is a striking fact that the pathologist can rarely make a diagnosis of cardiac failure by examination of the heart alone. As a rule the lesions of rheumatic,

hypertensive, arteriosclerotic, syphilitic and other forms of heart disease remain essentially the same in any one of the mentioned diseases whether or not the heart has failed. Frequently there is no evidence to indicate that the old valvular or myocardial lesions have undergone any recent change which might account for the onset of failure. There is often no close correlation between the extent of myocardial disease or the degree of valvular disturbance and the occurrence of cardiac failure. Extreme mitral stenosis, aortic stenosis or aortic insufficiency, or severe narrowing of the coronary arteries with myocardial fibrosis and necrosis is found at postmortem examination in persons who showed no clinical evidence of cardiac failure during life. Conversely the myocardium of persons with longstanding heart failure may show too few lesions to serve as an adequate anatomic basis for the clinical picture.

Sometimes, of course, as in cases of multiple coronary occlusions with extensive myocardial fibrosis and infarction or of diphtheritic myocarditis, there is no question that the extent and severity of the visible anatomic changes in the heart may account for the development of heart failure. Furthermore, on a statistical basis, the hearts in cases of cardiac failure show more conspicuous dilatation and hypertrophy, more severe degrees of valvular disturbance, greater coronary narrowing or more extensive myocardial disease than the hearts of persons with similar disease but without a clinical history of heart failure. Nevertheless there are so many instances in which there is a great disparity between the extent of pathologic changes in the heart and the clinical evidences of failure that the anatomic alterations in the heart cannot be considered a satisfactory, universal explanation for the occurrence of cardiac failure.

Conflicting Opinions as to the Significance of Microscopic Cardiac Lesions. The myocardial basis of cardiac failure was stressed particularly because of the microscopic investigations of Krehl,[26] Romberg[35] and other members of the Leipzig school of pathology. Krehl[26] studied eight hearts with valvular heart disease and found significant fresh and old macroscopic and microscopic lesions in the endocardium, pericardium, myocardium and vessels. In cases of typhoid fever, scarlet fever and diphtheria, Romberg[35] observed inflammatory lesions in the myocardium which he believed accounted for the symptoms of heart failure and the occasional occurrence of sudden death. In cases of idiopathic cardiac hypertrophy with symptoms of failure, Krehl[26] discovered inflammatory infiltrations, degenerative changes and extensive scarring. He concluded that heart failure was the result of these myocardial changes and not of the hypertrophy as such.

The concept that the pathologic changes in the heart accounted for the occurrence and onset of cardiac failure received its first major attack from the investigations of Aschoff and Tawara.[1] These observers showed that while inflammatory changes were often present in the myocardium in cases of rheumatic cardiovalvular disease, in many other cases of this disease and in the majority of other cases of chronic cardiac failure, significant inflammatory lesions were absent, or the changes were too slight to explain the development of heart failure. Certain so-called myocardial abnormalities such as a disproportion of sarcoplasm to myofibrils, pigmentation of fibers, perivascular round cells and degenerative nuclear changes were demonstrated to be either normal occurrences or artefacts. Aschoff and Tawara[1] concluded that, excepı

in diphtheria, heart failure in the majority of cases of cardiovalvular disease, nephritis, arteriosclerosis, infectious diseases, chronic pulmonary disease, syphilis, tumors or trauma, was due not to the extent of the anatomic myocardial lesions but to disturbances caused by increased functional demands on the heart.

Individual Pathologic Cardiac Abnormalities in Heart Failure. The following pathologic abnormalities have been described as a possible anatomic substratum for cardiac failure. Only brief comments are made as these changes are discussed in detail in the chapters on the individual etiologic diseases. In evaluating the following changes it is important to note (a) whether they are merely evidences of myocardial disease or indicative of cardiac failure, (b) whether their extent, severity or location can adequately account for the occurrence of cardiac failure and (c) whether the changes are the cause or the consequence of cardiac failure.

1. Inflammatory Lesions in the Myocardium. Rheumatic heart disease is the most important example of myocardial disease with predominant inflammatory lesions. But although the rheumatic lesions are usually widespread throughout the heart (p. 706), an essential feature is their localization in the interstitial tissue with relatively little involvement of the muscle parenchyma. It is difficult to understand how the observed pathologic changes can be responsible for heart failure when the active muscle appears intact. On the other hand, since cardiac failure appears frequently when there is *active* rheumatic myocarditis with or without significant valvular disease,[36] it is probable that the failure is due to some, as yet anatomically invisible, toxic, functional disturbance which accompanies the anatomic interstitial lesions and impairs myocardial function.

Similarly, interstitial inflammatory lesions of the heart appear in a variety of infections or infectious diseases which are occasionally accompanied by heart failure, but the pathologic lesions rarely appear adequate to explain the failure.

2. Degenerative Parenchymal Lesions in the Myocardium. Predominant degenerative changes of the myocardial fibers are seen in a variety of toxic and infectious diseases, in diseases of metabolism such as diabetes, in anemias and vascular disturbances. Usually these changes are not associated with cardiac failure. But even when cardiac failure develops, the anatomic lesions rarely appear to be an adequate cause.

Exceptions are seen in the instances of congestive heart failure associated with *myocardial necrobiosis.* Diphtheria is the classic example of myocardial failure apparently due to extensive destruction of myocardial fibers (p. 835). The interstitial inflammatory lesions seen in this disease are less important secondary changes which only appear if the disease lasts more than a week or two. In typhoid fever there are occasionally acute degenerative myocardial changes similar to Zenker's degeneration in the rectus abdominis and other striated muscles, but cardiac failure is rare. Fiedler's or isolated myocarditis, which is often complicated by heart failure, reveals essentially interstitial changes, but occasionally there is severe fatty degeneration, autolysis and even disappearance of large portions of the myocardial parenchyma. Coronary arteriosclerosis with occlusion is the most important cause of necrobiosis of heart muscle. Occasionally extensive areas of heart muscle are destroyed and

replaced by fibrous tissue; and in these instances there is a convincing anatomic basis for heart failure. Very often, however, heart failure develops without good correlation with the extent of the pathologic abnormalities.

Among *degenerative lesions of the myocardial parenchyma* are included cloudy swelling, fatty degeneration, vacuolar and hydropic degeneration, as well as necrobiosis. The concept of the fatty heart as a clinical-pathologic entity responsible for cardiac failure, heart block or sudden death has generally been discarded. Anemia or ischemia of the heart muscle definitely results in fatty change which appears as a characteristic linear streaking known as tigering. But when heart failure occurs in hearts showing tigering, there is usually an associated severe anemia or an arteriosclerotic or syphilitic coronary narrowing or occlusion which accounts for both the tigering and the failure.

Fatty degeneration of the heart is distinguished from *adipositas cordis* which usually appears in very obese persons. It is characterized by an excessive accumulation of pericardial fat which extends into and infiltrates the myocardium. There is insufficient evidence to indicate that this is ever an independent cause of heart failure.

3. Myocardial Fibrosis. The term chronic myocarditis was formerly applied to cases in which the heart revealed more or less extensive fibrosis of the myocardium. This term should be discarded because the fibrosis is rarely due to the healing of *chronic inflammatory lesions* as the name implies. As a rule the fibrosis results from ischemic necrosis of the myocardium due to (a) mechanical occlusion of a coronary artery, as in arteriosclerotic thrombosis, (b) severe narrowing of a coronary artery[2] or its ostium, as in arteriosclerosis or syphilis, or (c) relative coronary insufficiency when the blood supply does not keep pace with cardiac enlargement,[9] as in malignant hypertension and calcific aortic stenosis. Only occasionally is the fibrosis and replacement of myocardial tissue sufficient to account for heart failure.

4. Mechanical Defects of the Heart. The pathological lesions thus far considered have been situated in the myocardium. Often the essential or predominant lesions involve the valves or consist of congenital abnormalities of the septa or great vessels. These valvular or other defects usually place a disproportionate physical strain on one or more of the chambers of the heart. The importance of these defects is attested by the observations that the chamber primarily affected is the one which fails first, and that the type of heart failure, i. e., the clinical picture, is determined by the failure of the chamber in question. Thus with stenosis of the aortic valve the early symptoms of failure are determined by decompensation of the left ventricle, while with pulmonary stenosis it is the right ventricle which fails.

These and other observations indicate the importance of mechanical disturbances, independent of myocardial disease, in the development of cardiac failure. However, such mechanical strain cannot account for the instances of heart failure in which there are no valvular or other mechanical defects. Neither is it clear why failure occurs suddenly in hearts with old valvular defects which have not recently been altered or why failure may be absent in many cases with severe mechanical defects or present in cases where these are slight. Finally it should be emphasized that the cardiovascular abnormalities which increase the mechanical strain on the heart are usually associated with some myocardial disease, e. g., coronary artery sclerosis with essential hypertension; active rheumatic myocarditis with valvular defects, and in older

age groups coronary disease with rheumatic valvular defects; and syphilitic narrowing of the coronary ostia with syphilitic aortic insufficiency.

In conclusion, neither the character, extent nor localization of the visible macroscopic or microscopic cardiac lesions accounts satisfactorily for the development of cardiac failure in more than a minority of the cases. On the other hand, pathologic study in most cases reveals some myocardial, valvular or vascular abnormality which is the *underlying basis* of cardiac failure. We have yet to bridge the gap between this myocardial disease which underlies heart failure and heart failure itself. The visible anatomic abnormalities may be evidence only of some important deleterious but invisible changes in the function or structure of the contractile muscle tissue. In recent years the gap between cardiac disease and cardiac failure has been related to the pathologic physiology of cardiac dilatation and hypertrophy and the fundamental but invisible alterations in the muscle itself have been sought in chemical studies of the myocardium (infra).

Causes of Failure in the Enlarged Heart

The maintenance of normal cardiac function is dependent primarily on the functional capacity of the myocardium and the load against which it works. The cardiovascular diseases which eventually lead to congestive cardiac failure increase the load on the heart or depress its functional capacity or both. In Chapter 2 we have seen that cardiac dilatation and hypertrophy are the chief mechanisms by which the heart compensates (i. e., maintains its normal function) when either the mechanical load is increased or its anatomico-functional capacity reduced. In Chapter 3 we have noted that cardiac enlargement (dilatation and hypertrophy) occurs so often with cardiovascular disturbances that it is the cardinal clinical sign of cardiac disease. Numerous experimental clinical and pathologic observations indicate that cardiac enlargement is the response to cardiac disease and that cardiac failure is the end result of a variable period of increasing cardiac enlargement. Thus it has become epigrammatic that congestive heart failure is the failure of the enlarged heart. We will now consider the possible factors which cause the enlarged heart to fail.

1. Compensatory Limitation of Cardiac Enlargement. In disease as in health there is a limit beyond which the heart is incapable of compensating for circulatory strain. In health, the load of exercise may demand the maximum functional capacity of the heart, beyond which unpleasant symptoms compel the individual to desist. In disease the heart may be required to work continuously at or near maximum capacity because of the abnormal load of irreversible cardiovascular disease. This is accomplished by cardiac enlargement, but at the expense of cardiac reserve. Cardiac function of the enlarged heart may be adequate with the patient at rest but the lack of reserve prevents the increase in output which physical exertion demands. Eventually progressive myocardial disease, e. g., due to coronary arteriosclerosis, impairs the efficiency of myocardial contraction or diminishes the amount of available muscular tissue. Consequently cardiac compensation cannot be effected regardless of the degree of cardiac enlargement. The compensatory effectiveness of cardiac dilatation may be occasionally limited by the relatively indistensible pericardium but more often by progressive impairment of the physiologic fitness of the heart muscle.

In the heart-lung preparation Starling[41] found that the heart died within eight

to ten hours. Gradually the heart dilated as its functional ability deteriorated until the indistensible pericardium was filled and further dilatation was impossible. Thereafter further myocardial deterioration was evidenced by a fall in cardiac output and a rising venous pressure, i. e., heart failure.

Pathologic studies also suggest that heart failure often arises when cardiac enlargement reaches the limit of its compensatory capacity. Karsner, Saphir and Todd[23] found that the thickness of myocardial fibers could increase only to a relatively fixed dimension and that with increasing hypertrophy more and more of the fibers attained that maximum thickness. Postmortem observations also disclose that extremely heavy hearts are usually encountered only in subjects who had suffered from congestive heart failure. While cardiac enlargement is often observed without failure, *chronic* congestive failure is infrequently seen without pronounced cardiac enlargement. These observations appear to indicate that congestive failure usually develops when progressive cardiac enlargement reaches the limit of its capacity to compensate the cardiovascular strain. This compensatory limit varies greatly in different hearts, depending in part on differences in the contractile power and efficiency of the available heart muscle. In any case, as with skeletal muscle, there is an optimum beyond which further dilatation of the heart muscle is not accompanied by increased force of contraction.

2. Mechanical Inefficiency of the Enlarged Heart. Certain observations indicate that dilatation and hypertrophy, which arise as compensatory mechanisms, carry in themselves the germs of failure. Starling and Visscher[42] found in the heart-lung preparation and Moe and Visscher[30] in the completely isolated heart that when the heart began to weaken and dilate, its oxygen consumption increased in proportion to its degree of dilatation. This observation has been confirmed on the heart as a whole by Hemingway and Fee[18] and recently by Peters and Visscher.[32] Since the tiring, dilating heart continues to perform the same amount of useful work despite its increased oxygen consumption its mechanical efficiency is reduced below normal.[11, 8]

Because it is probable that Starling's Law of the Heart applies to humans, it may be assumed that the enlarged, diseased heart liberates more and more energy in proportion to its degree of enlargement. As the useful work of the enlarged compensated heart remains normal in terms of cardiac output, less and less of the increased total liberated energy is converted into useful energy during progressive cardiac enlargement. Thus in humans as in the experimental animal, the larger the heart, the less its mechanical efficiency. Mechanical inefficiency in itself does not necessarily cause cardiac failure. However it partially neutralizes the effect of increased energy liberation by the enlarged heart and thereby limits its compensatory potential.[12] According to another school of thought cardiac failure is not associated with a reduction in mechanical efficiency but with a decreased oxygen consumption for any given diastolic size, and therefore an inability to release energy.[37, 25]

3. Physicochemical Disadvantage of the Hypertrophied Heart. When the heart dilates as a result of cardiovascular disease, its muscle fibers become elongated so that a greater surface is available for physicochemical change. This is probably the mechanism by which it is enabled to perform the same amount of work as before the injury. But as we have seen, this is accomplished with a greater expenditure of energy and less efficiency. By some process still unknown

(possibly because of the greater oxygen consumption or greater surface for chemical change) dilatation is followed by hypertrophy. That is, the muscle fibers become thickened as well as lengthened and the diminished efficiency of the dilated heart is partly offset by a greater amount of muscular tissue. But now the thickened fibers of the hypertrophied heart offer greater difficulty to physicochemical exchange with their nutrient capillaries and tissue fluids than the thinner fibers of the normal heart.

The studies of Hill[21] have shown that the rate of diffusion of oxygen through tissues varies inversely as the square of the distance that the oxygen must traverse. Thus if the thickness of a muscle fiber is doubled, it would take four times as long for oxygen saturation of the fiber as before hypertrophy occurred. Harrison, Ashman and Larsen[16] found that the mean fiber thickness was 16.2 micra for normal hearts, 24.5 micra for the enlarged hearts of persons without congestive heart failure, and 31.8 micra for the enlarged hearts which had failed. These figures suggest that the fibers of the moderately hypertrophied heart are unable to obtain an optimal oxygen supply and are constantly in danger of anoxemia, while the fibers of the extremely hypertrophied heart are constantly suffering from some degree of anoxemia. This is particularly so in the central portions of the fibers which are furthest removed from the capillary twigs on either side.

This disadvantage of the hypertrophied heart with respect to oxygenation becomes intensified in the presence of tachycardia, such as accompanies physical exertion. For any given cardiac output, the oxygen requirement increases with an increase in cardiac rate.[3] At the same time tachycardia encroaches on the diastolic period during which almost all of the oxygen diffusion occurs. Persistent tachycardias due to disturbances in impulse formation and the tachycardia associated with fever and infection also exaggerate the impairment of oxygenation of the hypertrophied heart and may precipitate cardiac failure. The disadvantage of the hypertrophied heart with respect to the diffusion of oxygen probably applies also to the diffusion of other substances necessary for its nutrition and its performance of work, as well as to the elimination of waste products.

4. Deficient Blood Supply of the Enlarged Heart. The deficiency in oxygen diffusion through the hypertrophied muscle fibers is not compensated by a corresponding increase in the number of coronary vessels or in the amount of coronary blood flow. By the use of Krogh's equation for the tension differences necessary to cause oxygen diffusion between two points, Harrison[15] has estimated that the normal coronary flow is just about adequate to supply oxygen to the average-sized fiber of the moderately hypertrophied heart of a person at rest. But the average-sized fiber (about 40 micra) of the extremely hypertrophied heart would require a coronary blood flow two to three times as great as normal to receive proper oxygenation. With moderate exertion proper oxygenation might be entirely impossible.

A similar conclusion may be arrived at mathematically by considering each muscle fiber as a cylinder whose surface exposed to tissue diffusion is represented by 2π RL but whose volume of muscle mass is represented by πR^2L where R is the radius of its cross section and L its length. Using 16 micra as the diameter of the average normal muscle fiber, its exposed surface is $16\pi L$ and its volume $64\pi L$. In the greatly hypertrophied heart the fiber diameter may

average 32 micra, its surface being $32\pi L$ and its volume $256\pi L$. Thus while its active physicochemical surface through which nourishment may enter has been doubled, the mass of tissue to be nourished has been quadrupled.

Actually, anatomic studies fail to reveal an increase in coronary vessels or coronary blood flow which would be necessary to compensate for the increased requirements of the hypertrophied heart. Wearn[45] found an average of one capillary per muscle fiber in the normal heart. During hypertrophy the muscle fibers enlarge but the capillaries do not multiply; consequently the average number of capillaries per unit area in the hypertrophied heart is considerably lower than that in the normal heart.[31] Experimentally also, the Shipleys with Wearn[39] found that the capillary coronary supply did not increase with the development of cardiac hypertrophy in rabbits. Gross and Spark[14] noted that there was roughly an inverse relationship between the size of the heart and the number of arterioles and small arteries per unit area. In hearts weighing 200 to 300 gm. there was an average of 3.14 arterioles, whereas in hearts weighing 500 to 900 gm. there was an average of 1.13 arterioles per low power field.

Summary: Causes for Failure of the Enlarged Heart. Cardiac dilatation and hypertrophy start as compensatory processes which by their presence reveal the existence of cardiac disease. Increasing cardiac dilatation and hypertrophy mark the roadway from cardiac disease to cardiac failure. Cardiac enlargement (dilatation and hypertrophy) predisposes to cardiac failure because:

(1) It encroaches on cardiac reserve, which is limited by the ability of the muscle fibers to elongate and to become thicker. When the limit is reached, the heart can no longer compensate for additional mechanical strain or myocardial damage.

(2) The enlarged heart is less efficient mechanically than the normal heart because it consumes a greater quantity of oxygen although it performs the same amount of useful work.

(3) The thickened fibers do not permit as rapid a diffusion of oxygen, nutriments and metabolites as the normal fibers. In extremely hypertrophied fibers there is constant anoxemia even when a person is at rest. In moderately hypertrophied fibers anoxia occurs readily during exertion or with any arrhythmia or disease which increases the heart rate and reduces the diastolic period of recovery.

(4) The blood supply of the hypertrophied heart does not increase pari passu with its enlargement. Thus despite the greater requirement of oxygen because of the greater muscle mass to be nourished and the greater amount of total work, oxygen diffusion is impaired and there is no concomitant increase in the source of oxygenation. Thus there is a relative coronary insufficiency even when the coronary vessels are normal. This deficiency becomes greatly intensified in the course of years if the coronary vessels become narrowed by arteriosclerosis.

The Chemical Basis of Cardiac Failure

Ultimately the cause of cardiac failure must be sought in disturbances of the chemical processes which provide the energy for transformation into mechanical work. At the present time relatively limited observations are available which, it is to be hoped, represent only the beginnings of our knowledge in this important field.

Disturbances of the Glycogen Cycle. Glycogen is the major source of

energy for muscular contraction. There is evidence that relative anoxemia, present in the hypertrophied and failing heart, interferes with the aerobic oxygenation of lactic acid and the consequent energy formation required for the resynthesis of glycogen. Studies of experimental anoxemia[10, 24] and coronary occlusion[22] revealed a reduction of cardiac glycogen, especially in infarcted areas, and an accumulation of lactic acid in blood and muscle. Herrmann and Decherd[19] found a similar loss of glycogen in the infarcted areas of human hearts. Other observers have stressed the finding of increased lactic acid in the blood of patients with congestive heart failure,[29] particularly because of experimental evidence that the mammalian heart is much more readily exhausted by the accumulation of lactic acid than is skeletal muscle.[33, 24] However it is more probable that increased blood lactic acid is the result and not the cause of cardiac failure. A rise in the pyruvic acid concentration of the blood has been found in patients with congestive heart failure[47]; it probably has the same significance as the rise in lactic acid.

Disturbances of Phosphocreatine Metabolism. The fact that phosphocreatine is the *immediate* source of energy for muscular contraction and that it is reduced in skeletal muscle in certain forms of myasthenia and muscular dystrophies suggests that cardiac fatigue and failure may be due to a loss of myocardial phosphocreatine or to a disturbance in its metabolism. Since phosphocreatine is a very labile compound, it cannot be determined directly at autopsy, but creatine concentration may be taken as a measure of its quantity during life. A higher creatine concentration has been found in the left than in the right ventricle and this has been correlated with the greater strength of contraction of the former.[4, 38] However the difference in creatine concentration may be insignificant if allowance is made for the greater amount of extracellular water, fat and connective tissue in the right ventricle.

With slight increments in heart weight the creatine concentration was found to increase, but with progressive cardiac hypertrophy there was a corresponding reduction in creatine.[31, 5] In hearts of persons dying of congestive heart failure a substantial diminution in the cardiac creatine concentration has been uniformly observed.[5, 20, 27, 13] In cases of cor pulmonale the creatine concentration has been reported to be reduced in the right ventricle but not in the left.[27,28] The observed reductions in cardiac creatine in heart failure, like those of glycogen, have been related to deficient oxygenation, for similar low values for creatine in heart muscle have been found following asphyxia and myocardial infarction due to coronary artery occlusion.[20]

Phosphorus and Potassium Metabolism. Phosphorus and potassium concentrations in cardiac muscle have also been found to be reduced in congestive heart failure.[6, 17, 46] The total phosphorus in the heart consists of an acid soluble fraction (soluble in 5 per cent trichloracetic acid) and an acid insoluble fraction. The acid soluble fraction comprises the so-called "activity substances" including phosphocreatine, hexosephosphate, adenosine triphosphoric acids, all important in muscular contraction. It is this acid-soluble phosphorus fraction which accounts chiefly or entirely for the reduction in cardiac phosphorus in heart failure.[7] Potassium is the intracellular cation which is attached to the organic phosphoric acid compounds. Increased importance is being attached to the role of potassium in cardiac contraction and its possible relation to heart failure.[44, 11a]

The acid insoluble phosphorus fraction consists of lipids or phosphatids.

Various observers have noted a reduction in myocardial lipids in the fatigued experimental heart, and in the hearts of persons dying of heart failure. However there is some doubt as to whether the reduction in cardiac lipids is statistically significant. Theoretic importance has been attached to the cardiac lipoids because of their higher concentration in cardiac than in skeletal muscle and because of their active role in surface phenomena.

Adenosine Triphosphoric Acid. A reduction in adenosine triphosphoric acid in the hearts of patients dying of congestive heart failure has been revealed indirectly by determination of the nitrogen of the purines convertible to oxypurines.[27] The fact that the reduction of potassium and phosphorus exceeds the reduction in heart muscle creatine suggests also that this difference is due to a concomitant loss of adenosine triphosphoric acid, which like phosphocreatine contains phosphorus and is combined with potassium. Recent studies[43] indicating that muscular contraction occurs through physical changes in the actomyosin system, that potassium is released from actomyosin in the presence of acetylcholine and that the splitting of adenosinetriphosphate supplies the energy for recharging may also yield information as to cardiac contraction and myocardial disturbance in heart failure.

In summary, chemical studies of hearts of individuals who had died of heart failure indicate significant changes in those substances which are now considered of fundamental importance in muscular contraction. There is indirect evidence of a loss of myocardial glycogen and direct evidence of a reduction in myocardial creatine, total and acid soluble phosphorus compounds, potassium and possibly lipids.

PRECIPITATING CLINICAL CAUSES OF CONGESTIVE HEART FAILURE

While the fundamental cause for the onset of congestive heart failure is still obscure, a clinical precipitating factor can often be determined. Of 100 cases of cardiac failure studied by Sodeman and Burch,[40] failure was precipitated by some demonstrable factor in 53 while in 47 it developed gradually without apparent cause.

1. Infections. Myocardial failure in the cardiac patient is very often precipitated by (a) infections which directly increase the myocardial disease or (b) intercurrent infections which incidentally impair cardiac function or otherwise induce heart failure.

(a) Rheumatic fever is the prime example of an infection which may cause cardiac failure by direct action on the heart. Rheumatic fever is the commonest cause of cardiac failure between the ages of 10 and 40 and is an important cause even after 40. The occurrence of heart failure after a more or less prolonged period of inactive rheumatic heart disease is not infrequently associated with recurrent rheumatic activity. The studies of Rothschild, Kugel and Gross[36] on 161 rheumatic hearts of persons who had died of congestive heart failure showed that up to the age of 20, 95 to 100 per cent of the hearts revealed signs of active rheumatic carditis, between the ages of 20 and 40 about 75 per cent disclosed such signs, and even after the age of 40, cardiac failure was associated with active rheumatic myocardial lesions in one fourth of the cases. Nevertheless, beyond the age of 40 and especially after 50, other factors seemed more important than rheumatic activity in the precipitation of heart failure in rheumatic hearts.

(b) Intercurrent infections, especially those of the respiratory tract, very

often lead to the development of congestive heart failure, but usually only in patients with preexistent chronic cardiac disease. It should also be emphasized that upper respiratory infections predispose to attacks of rheumatic fever and thus indirectly cause cardiac failure. Subacute bacterial endocarditis is not infrequently complicated by congestive cardiac failure either because of concomitant activation of rheumatic fever or because of increased valvular deformity and myocardial damage.

The mechanisms by which infections, especially respiratory infections, may induce cardiac failure are: (1) Increased work of the heart due to fever and tachycardia. (2) Toxic effect on the myocardium which is not demonstrable anatomically. (3) Diminution of the diastolic period of recovery because of tachycardia. This factor is particularly harmful in the hypertrophied heart. (4) Cough in respiratory infections may represent intense muscular exertion and a severe strain on the heart in persons with cardiac disease. (5) Infections may be associated with impairment of renal excretion of sodium.

2. Inadequate Coronary Blood Flow. We have already discussed the theoretical importance of a diminished coronary blood flow in causing cardiac failure. In emphasizing that it is usually the large heart which fails, we considered the relatively inadequate coronary blood flow and impaired diffusion of oxygen to the hypertrophied fibers and the effect of the resulting anoxemia on cardiac metabolism. We often observe the cardiac patient who remains well compensated until coronary artery disease develops in middle or old age. In rheumatic cardiovalvular disease, in hypertension and in luetic aortic insufficiency, cardiac failure often develops only when coronary arteriosclerosis (narrowing or occlusion) adds its baneful influence to that of valvular or cardiovascular disease. In these cases the cardiac hypertrophy is an effective compensatory mechanism until coronary insufficiency interferes with the increased needs for oxygen. In addition, acute coronary occlusion, by causing extensive damage to heart muscle, may precipitate failure in a heart which was not previously enlarged.

3. Changes in Rate and Rhythm. Paroxysmal tachycardia, in which the heart rate is often 200 per minute or more, occasionally precipitates congestive heart failure if the attack is prolonged. As a rule this occurs in patients with underlying organic heart disease, but occasionally it may occur in the presence of a normal heart. Rapid ventricular rates (over 100) with auricular fibrillation or auricular flutter often lead to failure of the diseased heart or at least are associated with the onset of cardiac failure. Tachycardia interferes with myocardial contraction not only by preventing proper oxygenation in an hypertrophied heart, but also, when the rate exceeds 180 per minute, by seriously reducing the diastolic recovery period and preventing adequate cardiac filling.

4. Pregnancy and Childbirth. Heart failure sometimes develops in the course of childbirth or pregnancy in patients with previous heart disease (Chapter 47). Acute pulmonary edema is occasionally observed in patients with mitral stenosis and pulmonary congestion. It is now recognized that in persons with well-compensated heart disease heart failure during pregnancy and childbirth occurs with extreme infrequency. On the other hand, in patients with previous attacks of heart failure or in those with limited cardiac reserve, congestive heart failure occurs commonly. The possible mechanisms are discussed in Chapter 47.

5. Hemorrhage and Anemia. Anemia is not infrequently associated with

cardiac enlargement and sometimes with congestive heart failure. In persons with chronic cardiac disease, heart failure may be induced by progressive anemia or acute loss of blood. I have seen heart failure precipitated in two patients with hypertensive and arteriosclerotic heart disease and in one with rheumatic cardiovalvular disease immediately after an acute hemorrhage due to a peptic gastric or duodenal ulcer. I have also seen cardiac failure develop in a patient with hypertensive cardiovascular disease with a hemoglobin of 17 per cent due to a chronic bleeding hemorrhoid. These precipitating factors of cardiac failure are important to recognize because they can sometimes be prevented. Treatment may beneficially affect the manifestations not only of the anemia but of the heart failure.

6. Pulmonary Embolism. I have repeatedly observed cardiac failure induced by pulmonary embolization, especially in patients with rheumatic heart disease. In some instances persistence or recurrence of heart failure is related to repeated embolization. In many of these cases the precipitation of heart failure is erroneously attributed to bronchopneumonia.

7. Transfusions and Sodium-containing Infusions. These not infrequently precipitate heart failure in patients with organic heart disease and in elderly patients without overt evidence of previous heart disease. They may also induce heart failure in patients with acute glomerulonephritis, toxemia of pregnancy or toxic nephrosis with severe oliguria or anuria.

8. Physical and Emotional Strains. *Acute* overexertion occasionally initiates congestive heart failure and then only in persons with diseased hearts. It is uncertain to what extent *prolonged* overexertion contributes to the occurrence of heart failure. Sodeman and Burch[40] and others list exercise as the most common precipitating factor of cardiac failure, but it is not clear what degree or form of exercise is responsible or what is the exact relationship to failure. Insurance statistics which indicate that long-continued and strenuous labor adversely affects the heart fail to account for many associated factors such as differences in constitution, heredity and social and economic status.

Occasionally heart failure appears to be precipitated by experiences which involve considerable physical and emotional strain. For example, pulmonary edema or other evidences of congestive heart failure may appear after surgical operations, coitus and prolonged worry and anxiety. Surgical operations may lead to coronary insufficiency or myocardial infarction with subsequent heart failure as a result of a drop in blood pressure and shock. The tachycardia and elevation of blood pressure may be the factors responsible for heart failure after coitus. In both of these as well as in various states of fear and anger the cardiac output and work of the heart may be increased.

Significance of the Precipitating Causes of Congestive Cardiac Failure

It is important to recognize the *precipitating* causes of heart failure for we can more readily avoid or eliminate these causes than we can other factors in the development of heart failure. For the present, the avoidance of these precipitating factors offers the most direct and the most promising approach to the prevention or postponement of heart failure. The fundamental basis of heart failure is still obscure, while the underlying causes are usually not susceptible either of prevention or treatment.

Recognition of the precipitating cause of cardiac failure is important in the

prognosis as well as treatment of this condition. Sodeman and Burch[40] found that of 47 cases of cardiac failure without recognizable precipitating cause 46 were unable to restore cardiac compensation despite treatment. On the other hand, of 54 cases with a demonstrable precipitating factor, compensation was rapidly established in 40. Thus the outlook in a given case of heart failure is much better when a definite precipitating factor is present.

UNDERLYING CAUSES OF CONGESTIVE HEART FAILURE

For practical as well as theoretical reasons we have segregated the fundamental cause, the precipitating causes and the underlying causes of congestive heart failure. In considering the fundamental cause, we attempted to investigate the *mechanism* or bridge by which the diseased and occasionally the normal heart becomes the failing heart. The precipitating causes include the clinical conditions which, because of their close sequential relationship, appear to be concerned in the onset of the symptoms of heart failure. The underlying causes of heart failure comprise those diseases which injure the pericardium, myocardium, valves or peripheral vessels and thereby bring about functional and anatomic changes in the heart or vascular system which eventually lead to cardiac failure. In other words the underlying causes of heart failure are the various specific forms of cardiovascular *disease* as contrasted with the forms of cardiovascular *failure*. These underlying causes are considered in detail in subsequent chapters in this book.

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5

CLINICAL AND PATHOLOGIC FEATURES OF CHRONIC (CONGESTIVE) HEART FAILURE

Congestive heart failure is essentially a *clinical* syndrome. From the physiologic viewpoint heart failure represents an inability of the heart to maintain an adequate output. But it is difficult to measure this disability in clinical practice. Furthermore, because of compensatory mechanisms the cardiac output may sometimes remain normal despite the presence of heart failure (Chapter 6). The manifestations of congestive heart failure are only exceptionally directly due to an inadequate cardiac output; as a rule they are the consequences of the compensatory mechanisms. Congestive heart failure is defined and recognized by the presence of distinctive clinical features which are the subject of this chapter.

LEFT-SIDED HEART FAILURE

While the normal heart appears to act as a single pump, the left and right chambers are really distinct anatomic and functional entities. Under pathologic circumstances, one side or even one chamber of the heart may fail while the other side is still functioning normally. Sooner or later failure of one side of the heart places a strain on the remainder which eventually leads to generalized cardiac failure, but for a variable period isolated left-sided or isolated right-sided heart failure may exist as a distinct and independent clinical syndrome.

Failure of the left side of the heart is the most important and most common form of congestive heart failure encountered in medical practice. The existence, the pathogenesis and the clinical features of left-sided heart failure were noted by Hope[29] and by a succession of French physicians.[41] In recent years the importance of the syndrome of left ventricular failure was stressed and its clinical features described in this country by Pratt,[59] White,[71] Weiss and Robb,[69] and others, in France by Gallavardin[20] and by Lutembacher[42] and in England by Bedford.[3]

Causes of Left-Sided Heart Failure

Left ventricular failure results from those cardiovascular diseases which injure or strain the left ventricle, namely hypertension, coronary artery disease and aortic valvular disease. Bedford[3] observed 154 cases of left ventricular failure, in 132 of which the failure was paroxysmal and in 22 persistent or

terminal. In the group of 132, 111 patients suffered from hypertension, associated in 43 with angina pectoris or coronary thrombosis; 12 patients suffered from coronary disease without hypertension; 21 suffered from aortic valvular disease. There were only a few cases of syphilitic aortic insufficiency.

Left atrial failure results from mitral stenosis which is almost invariably caused by rheumatic heart disease. It is seen among earlier age groups than is left ventricular failure. Left atrial failure is seen predominantly among females and left ventricular failure among males. These and other factors in the etiology of left-sided heart failure are related not to the heart failure itself but to underlying causative diseases. For this reason details as to etiology should be sought in the chapters devoted to these diseases.

Pathologic Physiology of Left-Sided Heart Failure

The pathogenesis of the clinical picture of heart failure has been the subject of so much recent discussion that the proposed theories and the author's views are considered in detail in a subsequent chapter (Chapter 6). The pathogenesis of the individual symptoms is discussed in Chapter 7. These have been deferred until the clinical picture itself could be depicted.

For purposes of preliminary orientation it may be stated here that left-sided heart failure arises when dilatation and hypertrophy of the left atrium and/or the left ventricle cannot restore an adequate cardiac output. Compensatory mechanisms, in which the renal excretion of sodium and water are involved, result in an increased circulating blood volume and a consequent augmentation of the venous return. The reserve power of the normal right ventricle permits it to accept and expel this increased inflow of blood. But when the increased venous return arrives at the failing left side of the heart, it cannot be completely expelled. This results first in an increased volume and pressure of blood in the left heart and then in a damming of blood and a rise of pressure in the pulmonary veins and capillaries.

The increased pressure helps to restore the output of the left heart and to equalize it with that of the right chambers. These compensatory mechanisms result in an increased systolic and diastolic volume of blood in the left chambers and an increased blood volume in the lungs. The adequacy of the left cardiac output may again be disturbed during physical exertion which leads temporarily to an enhanced venous return and an increased right cardiac output into the already engorged lungs.

Most of the manifestations of left-sided heart failure result from the increased pulmonary blood volume and consequent engorgement of the lungs (Chapter 7). Among the resulting physiologic disturbances are the rigidity and loss of elasticity which interfere with normal inspiratory and expiratory movements, reduction in vital capacity, impairment of diffusion of oxygen and slowing of the pulmonary circulation. The last is actually beneficial because it compensates for impaired diffusion by permitting a longer period for each unit of blood to absorb oxygen and release carbon dioxide.

Pathology of Left-Sided Heart Failure

The pathology of left-sided heart failure is essentially the pathology of engorged lungs (passive congestion of the lungs). The lungs appear somewhat different when the engorgement results from left ventricular failure in hypertensive, coronary artery or aortic valvular disease than when it results from

left auricular failure in cases of mitral stenosis. The differences are due to the more gradual development and the much longer duration of the pulmonary engorgement with mitral stenosis. The latter is described in detail in the chapter on mitral stenosis (p. 565).

The lungs in left-sided heart failure are usually larger and firmer than normal, and do not collapse readily when the chest wall is opened, because of increased content of blood and therefore diminished elasticity. In cases of left ventricular failure the lung is usually dark red, and "wet" in that bloody or frothy fluid may be expressed easily by squeezing or scraping of the surface or by cutting into the lung. In cases of longstanding pulmonary congestion, e. g., in mitral stenosis, the lung is usually dry and indurated due to fibrosis, and brown due to deposition of hemosiderin following phagocytosis of extravasated erythrocytes (brown induration of the lungs).

Microscopically[31, 55] the lungs reveal engorgement and widening of capillaries with encroachment on alveoli, thickening of alveolar septa, extravasation of large mononuclear cells (heart-failure cells) containing erythrocytes or the reddish granules of the iron pigment, hemosiderin.

Other frequent findings in the lungs include pulmonary *emboli and infarcts, hemorrhages,* hypostatic congestion, *bronchopneumonia* and bronchitis.

Clinical Features of Left-Sided Heart Failure

Symptoms. *Exertional Dyspnea and Dyspnea at Rest.* Dyspnea (breathlessness, shortness of breath) denotes the subjective respiratory distress associated with increased effort in breathing. When mild it may be purely subjective and discovered only by specific inquiry or from the patient's voluntary complaint. When more severe, there may be objective evidence of increased respiratory effort such as interrupted, breathless speech, frequent stops during walking or climbing stairs, dilatation of the alae nasi or when very severe, the use of the accessory muscles of respiration.

Dyspnea during ordinary exertion is usually the earliest symptom of left-sided heart failure. The dyspnea may be minimal in the morning and may progress gradually until it is quite disturbing by the time the patient retires at night (evening dyspnea[27]). At first dyspnea occurs only with moderately severe exertions such as running for a bus or train, walking up a hill or climbing several flights of stairs. Gradually, or more rapidly (e. g., after an infection or coronary occlusion), the dyspnea becomes more severe and appears with less and less strenuous activity. The patient then experiences breathlessness even when walking along level ground and is compelled to rest frequently in order to get his breath. Finally dyspnea may persist even when the patient is at rest in bed.

Of interest is the frequent alleviation of dyspnea when the right heart also fails. Conversely, in combined right and left-sided heart failure the administration of digitalis and diuretics sometimes leads to an initial intensification of dyspnea as the mobilization of edema fluid and right ventricular improvement lead to an augmented output into the pulmonary vascular tree.

The subjective nature of mild dyspnea sometimes makes it difficult to evaluate. Cardiac dyspnea is of a panting or puffing quality and not merely an "inability to take a deep breath." Objectively cardiac dyspnea is characterized by rapid, shallow respirations in contrast with the deep breathing of diabetic or uremic acidosis. When dyspnea is caused by heart failure, it is precipitated by exertions previously performed without discomfort; factors such as increasing

obesity, change to sedentary occupation, pregnancy, pulmonary disease, etc., must be excluded.

Pathogenesis of Dyspnea (see p. 106).

Orthopnea. Orthopnea is the form of dyspnea which occurs when the patient assumes a recumbent position. To avoid respiratory distress on going to bed he elevates the head and chest with two or three pillows. Sometimes he unconsciously adopts a semi-sitting position while asleep. When the orthopnea is severe, the patient may have to be propped straight up in bed or he may obtain comfort only by sitting at the edge of the bed with his feet hanging; often his head and neck are flexed forward and his hands clutch the side of the mattress in order to aid the accessory muscles of respiration. He may spend most or all of the night in a chair because this offers the best support and the least recumbency.

These positions tend to relieve orthopnea by diminishing pulmonary congestion and increasing pulmonary ventilation (p. 112). In patients with continuous dyspnea and orthopnea, breathlessness persists even after sitting up but it is usually less intense than in the recumbent position. In some persons orthopnea occurs in one recumbent position (e. g., the left lateral) but not in another (e. g., the right lateral). This selective type of orthopnea, which has been termed trepopnea,[75] is probably the result of greater pulmonary engorgement in the first position than in the other.

Orthopnea may be noted at night in persons who have suffered no exertional dyspnea during the day. I have seen patients with valvular heart disease who have had to sleep on two or three pillows at night because of orthopnea, and yet continued for several years to conduct their business during the day without noticeable dyspnea.

Pathogenesis of Orthopnea (see p. 112).

Paroxysmal Dyspnea. Paroxysmal dyspnea refers to the respiratory distress which appears in attacks without apparent cause. Because such attacks usually occur at night after the patient has fallen asleep, they are often called paroxysmal nocturnal dyspnea. The term cardiac asthma is employed synonymously with paroxysmal dyspnea because the wheezing character of the respiration and the signs in the lungs resemble those in bronchial asthma. Paroxysmal dyspnea usually occurs in patients who are suffering also from exertional dyspnea and from orthopnea. Occasionally persons who are fairly comfortable and have little or no dyspnea during ordinary activity by day are intensely distressed by nocturnal dyspnea. Paroxysmal dyspnea is relatively uncommon with left atrial failure in cases of mitral stenosis.

The *attack of paroxysmal dyspnea* almost invariably occurs about an hour or two after the patient has retired and fallen asleep. Diurnal attacks also occur while the patient is asleep. The *precipitating cause* of the attack is uncertain and probably variable. Cough, bad dreams, slipping of the patient from his pillows to a more recumbent position, turning to the side on which he is ordinarily dyspneic, abdominal distention are among those suggested.

The attack varies greatly in severity and duration. In mild cases the patient awakens with a sense of respiratory distress or suffocation often associated with anxiety. To obtain comfort he may merely sit up in bed or sit at the edge of the bed with his feet hanging. In other instances the patient pleads to have the windows opened further or sits in a chair beside the open window because of the mistaken feeling that there is insufficient air in the room. In the mildest

cases relief is obtained a few minutes after sitting up. Often the attack ends immediately after coughing up and expectorating blood-tinged mucus. In the less mild cases relief may not occur for half an hour to an hour. In the relatively mild cases the physician may not be summoned at all or the attack may have subsided by the time the physician arrives.

In severe attacks of paroxysmal nocturnal dyspnea, the respiratory distress is much more intense and prolonged. The patient is found sitting upright in bed trying desperately to get more air by the use of the accessory muscles of respiration. The breathing is rapid and usually deep. Sometimes it is noisy due either to audible asthmatic wheezes[54, 57] or to bubbling or gurgling sounds caused by moisture in the lungs. As a rule the respiration is regular, but it may have periodic variations. Occasionally attacks follow each other in rapid succession—a cardiac form of status asthmaticus. The attack usually yields dramatically to a hypodermic injection of morphine and other therapeutic measures (see p. 207). The next morning the patient may feel as well as before the attack but more often he is exhausted and breathless. Occasionally a severe or protracted attack of paroxysmal nocturnal dyspnea ends fatally, usually with the development of extensive pulmonary edema.

Pathogenesis of Paroxysmal Dyspnea (see p. 113).

Pulmonary Edema. Clinical manifestations of pulmonary edema are usually observed in patients suffering from cardiac asthma. Often pulmonary edema accompanies or complicates the attacks of paroxysmal dyspnea. But it may appear for the first time in persons who have never experienced any form of dyspnea, e. g., after an attack of coronary artery occlusion, an hypertensive crisis, or after transfusions or intravenous infusions.[48, 65] A slight degree of pulmonary edema is probably present during most attacks of cardiac asthma, but a characteristic clinical picture is produced only with massive edema of the lungs. Like cardiac asthma, pulmonary edema usually occurs in patients with left ventricular failure secondary to coronary artery disease (especially coronary occlusion), hypertension and aortic valvular disease. Pulmonary edema occurs very uncommonly with mitral stenosis, usually as a complication of pregnancy or labor, undue physical exertion, sexual intercourse or a pneumonic infection.

The *clinical picture of acute pulmonary edema* is characterized by intense dyspnea, orthopnea, cough and extreme anxiety. The breathing is always noisy either because of loud inspiratory and expiratory wheezes or audible gurgling or bubbling sounds. There is always a fair amount of sputum but in severe attacks the patient drowns in the profuse secretions which may pour from the nose as well as the mouth. The sputum is usually frothy and may be colorless, but as a rule it is pink-stained because of the presence of blood. The sputum is unusually rich in protein, the concentration of which may be as high as 2 to 3 per cent.

The patient is cyanotic, especially if the attack is prolonged, and often his skin is covered by a cold sweat. He may suffer from intense precordial oppression or actual pain. The blood pressure is usually elevated unless there is shock. The pulse is full but if relief is not obtained it becomes rapid and thready. As in cardiac asthma, the physical signs are those of intense pulmonary emphysema (p. 895). But whereas with cardiac asthma there may be no râles or only crepitant or subcrepitant râles at the extreme bases of the lungs, with definite pulmonary edema there are moist subcrepitant râles over extensive areas or

throughout the lungs. There are often also coarse, bubbling râles which may be heard even without examining the patient.

The attack of pulmonary edema may be relatively mild or very severe. It usually subsides spontaneously after a few minutes or hours, often following the coughing up of some blood-stained, frothy sputum. Frequently the attack is dramatically and rapidly controlled by an injection of morphine, the application of tourniquets to the extremities or a generous venesection. Except for temporary exhaustion, the patient is usually rapidly restored to the same condition as before the attack. While any given attack usually subsides spontaneously or with treatment, acute pulmonary edema may end fatally in its first or some subsequent episode.

Pathogenesis of Pulmonary Edema (see p. 114).

Cheyne-Stokes Respiration. This is a periodic form of breathing characterized by waxing and waning of the depth of respiration and by regularly recurrent periods of apnea.[13, 67] Left ventricular failure is most likely to be associated with Cheyne-Stokes respiration when it occurs in elderly persons with hypertension and cerebral arteriosclerosis who have received opiates or large doses of sedatives. It may appear in association with the Stokes-Adams syndrome. It is not a specific symptom of heart failure and occurs in a variety of cerebral diseases. Biot respiration, which is seen in patients with increased intracranial pressure, is distinguished by identical depth of each respiration, irregular respiratory periods and only four or five breaths to each period.[14]

In the typical Cheyne-Stokes respiration several hardly perceptible shallow respirations gradually and rhythmically deepen into respiratory excursions of normal depth. After a half dozen such, the respirations become deeper and deeper until they are abnormally exaggerated, following which they again gradually subside until they are hardly perceptible. This respiratory cycle, comprising thirty or more respirations, consists of phases of crescendo and diminuendo, which occupy one to three minutes. Often the shallow respirations shade off into a period of apnea which may last ten to thirty seconds or longer. Prolonged apneic periods may be associated with deepening cyanosis and muscular twitchings of the face and extremities. Cheyne-Stokes respiration may be accompanied by periodic changes in cardiac rhythm, including sinus slowing, nodal rhythm and various degrees of heart block.

Pathogenesis of Cheyne-Stokes Respiration (see p. 116).

Cough. Cough is almost invariably present with the acute paroxysms of dyspnea and with pulmonary edema in patients with left-sided heart failure. It may also be a significant symptom in the intervals between such attacks. It is often worst at night or occurs only at that time. Insomnia may be due to the cough. Sometimes the cough of heart failure, like dyspnea, may be induced only by exertion or recumbency. The cough may be secondary to the pulmonary engorgement, to chronic passive congestion of the bronchial mucous membrane or to pulmonary infarction or bronchopneumonia. Of special interest are instances of left heart failure in which cough dominates the symptomatology and dyspnea is overlooked. I have frequently observed such patients treated for bronchopulmonary disease. It is important to recognize that a bronchitis in elderly persons is often an evidence of congestive heart failure. Fever may be absent or only of slight degree. Harrison, Calhoun and Harrison[27] have emphasized the significance of cough not only as a symptom of left-sided heart failure

but as a factor in precipitating cardiac asthma, intensifying dyspnea when present, and in increasing the strain on the right ventricle by elevating the pulmonary arterial pressure.

Cough is an important symptom in certain forms of cardiovascular disease, even in the absence of heart failure. It is observed in cases of luetic aneurysm with compression of trachea or bronchus, of mitral stenosis with very large left atrium or pulmonary artery compressing a bronchus or of a congenital double aortic arch forming a vascular compression ring around the trachea.[36, 17]

The cough is usually accompanied by mucopurulent expectoration. In attacks of cardiac asthma and pulmonary edema, the sputum is characteristically frothy and pink due to the presence of small amounts of blood. In cases of mitral stenosis with pulmonary congestion the sputum is often rusty because of its content of hemosiderin-bearing "heart-failure cells." When infarction of the lung occurs in left-sided heart failure, the sputum is often extremely tenacious and blackish-red or it may be frankly bloody.

Hemoptysis. The expectoration of blood or bloody sputum in mitral stenosis and pulmonary edema has been mentioned.[51] In cases of left heart failure it is often due to an associated pulmonary embolism and infarction.

Cyanosis. Cyanosis of mild degree is often present in pure left-sided heart failure, but it is not a characteristic feature. It is an early and frequent symptom of the pulmonary congestion due to mitral stenosis.[15] Cyanosis may be prominent in left ventricular failure when there is acute pulmonary edema or when there are complications such as bronchopneumonia, pulmonary embolization or a coincident pulmonary emphysema.

Pathogenesis of Cyanosis (see p. 123).

Hoarseness. Hoarseness is a rare symptom of left-sided heart failure and has been attributed to paralysis of the left recurrent laryngeal nerve as a result of compression by a dilated pulmonary artery.[35]

Physical Signs of Left-Sided Heart Failure. *The Heart.*

ENLARGEMENT OF THE HEART may be revealed by inspection and palpation of the apical impulse, by percussion and by roentgenologic examination.

GALLOP RHYTHM.[58, 28] This is a triple sequence of sounds suggesting a horse's gallop. The effect is created by a distinct extra sound, the gallop sound. It is of dull quality and low pitch and differs from a split or reduplicated sound because there is a more distinct interval between the gallop and neighboring sounds. The gallop sound can be felt as well as heard. The succession of palpable sounds may present a characteristic sensation to the fingers which is known as tremor cordis. The gallop sound in left heart failure is either protodiastolic or presystolic in time. This is most clearly revealed by phonocardiography[74] (Fig. 19).

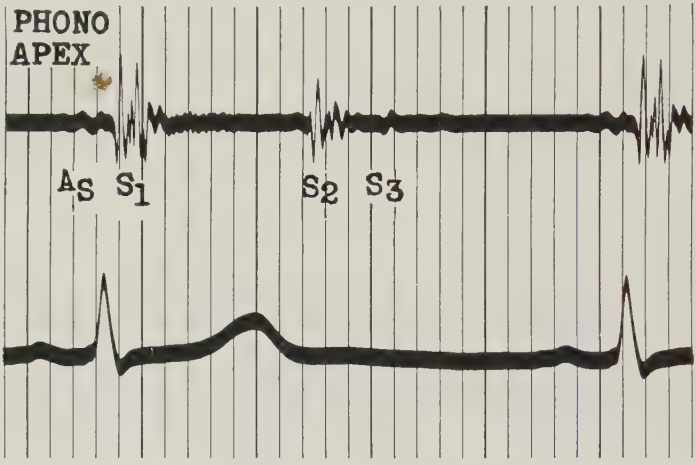
Gallop rhythm is usually heard only or heard best near the apex of the heart, but it may be present to the left of the lower sternum or occasionally in other parts of the precordium. Since gallop rhythm is audible, as a rule, only in the presence of tachycardia, it may be brought out by having the patient exercise. The gallop is most distinct in deep expiration and with the patient on his left side. As a rule gallop rhythm does not occur or disappears with auricular fibrillation[9] but there are exceptions.

Pathogenesis of Gallop Rhythm (see p. 126).

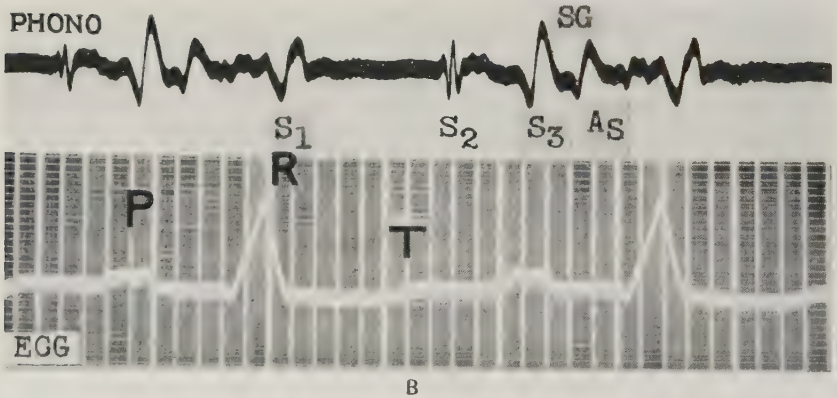
ACCENTUATION OF THE SECOND PULMONIC SOUND is due to the high tension

in the pulmonary artery in left-sided heart failure.[6] The second pulmonic sound may become louder than the second aortic even when there is pronounced systemic hypertension.

An APICAL SYSTOLIC MURMUR is frequently present due to a relative mitral insufficiency. Tachycardia is frequent. Tic-tac sounds (embryocardia) may



A



B

Fig. 19. *A*, Normal heart sounds. Upper tracing phonocardiogram at apex. Lower tracing simultaneous electrocardiogram. S_1 = first heart sound, A_S = auricular sound of low amplitude, inaudible as distinct sound, S_2 = second heart sound, S_3 = third heart sound. A functional systolic murmur, inaudible to ear, follows the first sound in this phonocardiogram.

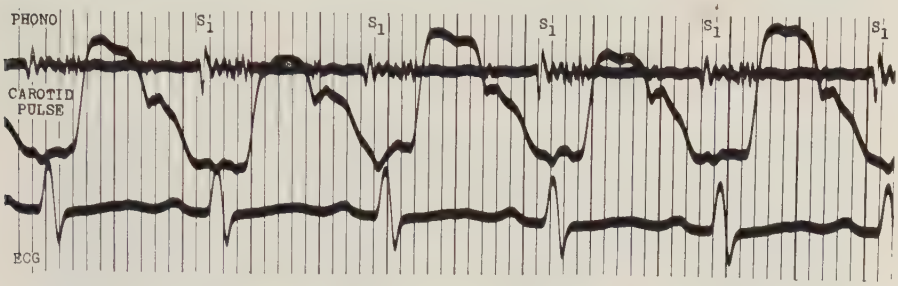
B, Gallop rhythm. Exaggerated S_3 causes diastolic gallop sound. Exaggerated A_S causes presystolic gallop sound. Their proximity in this case caused a fusion or summation gallop sound (SG) in diastole.

result from shortening of diastole by tachycardia with consequent even spacing of the two sounds. *Auricular fibrillation* is frequent.

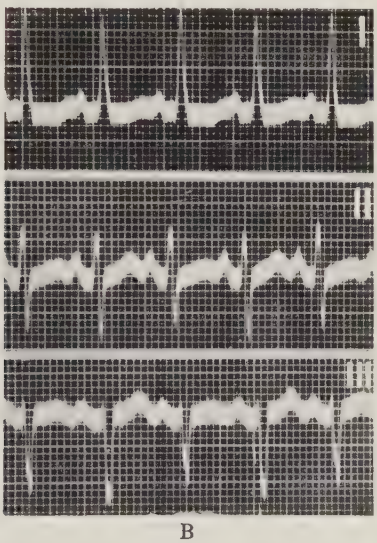
CARDIAC SIGNS OF THE UNDERLYING DISEASE. These are discussed under the individual headings of hypertension, aortic stenosis, etc.

ALTERNATION OF THE PULSE may be a sign of left ventricular failure. It is

recognized by inflating the cuff to the systolic pressure. As the cuff is very slowly deflated, only alternate beats are heard for a distance of 2 to 10 or more mm. Hg below the systolic level.[70] Rarely pulsus alternans is recognizable by palpation of the radial pulse; unlike premature beats of pulsus bigeminus, the weak beat is very slightly closer to the succeeding beat than to the preceding one. The heart sounds do not usually appear to be modified,[73] but graphic records have demonstrated such alternation in intensity of the sounds[16] (Fig. 20*A*). Alternation of the amplitude of contraction has been demonstrated by roentgenkym-



A



B

Fig. 20. *A,* Alternation in intensity of heart sounds and pulsus alternans. Upper strip = phonocardiogram, middle strip = carotid pulse, lower strip = simultaneous electrocardiogram.

B, Electrical alternans. Alternating variations in height of R waves best seen in lead III.

ography.[64] Alternation of the QRS or T wave or of any other wave in the electrocardiogram may be associated with pulsus alternans. This is termed electrical alternans (Fig. 20*B*). It may be absent when the pulsus alternans is present or it may occur in the absence of pulsus alternans.

Pathogenesis of Pulsus Alternans (see p. 127).

The Lungs. BASAL RÂLES AND EMPHYSEMA. Usually the signs are those of a functional emphysema, as noted particularly by Weiss and Robb.[69] Between

attacks of cardiac asthma or pulmonary edema, there may be no râles or only a few crepitant or subcrepitant râles at the bases of the lungs posteriorly. The râles are occasionally unilateral or predominantly on one side. During or immediately after an attack of cardiac asthma there may be many sonorous or sibilant râles resembling the rhonchi of bronchial asthma. With pulmonary edema, fine and coarse moist râles become more extensive and the entire chest may be filled with bubbling or gurgling sounds. In addition there may be signs of a complicating bronchitis, bronchiectasis, bronchopneumonia or pulmonary infarction. Pulmonary infarcts are almost always bland and disappear completely. But occasionally they undergo suppuration.[56]

HYDROTHORAX. According to Bedford,[3] hydrothorax occurred in 25 per cent of his 154 cases of left-sided heart failure. A pleural effusion, which often



A B

Fig. 21. *A*, Chronic venous congestion of the lungs in heart failure. Diffuse haziness of lung fields especially lower lobes. Prominent hilar vessels. Cardiac enlargement. *B*, Congestive heart failure with venous stasis in lower lobes and bilateral hydrothorax. Pulmonary infarct of right lower lobe may be obscured by pleural effusion.

contains blood, may follow pulmonary infarction.[38] Unlike the fluid of hydrothorax this effusion has the characteristics of an exudate. Occasionally an encapsulated interlobar effusion is seen.[2, 7] Usually hydrothorax in the course of congestive heart failure appears predominantly or exclusively on the right side,[44] but in Bedford's[3] cases of left-sided heart failure the pleural effusion more often involved the left pleural cavity. For further discussion see p. 121.

REDUCTION IN VITAL CAPACITY. The vital capacity (p. 109) as well as the total pulmonary air space is greatly diminished.[69] On the other hand the residual air space is notably increased. There is a rough parallel between severity of dyspnea and reduction in vital capacity.

Roentgenologic Appearance of the Heart and Lungs in Left-Sided Heart Failure. The *hilar shadow* is often increased both in density and width. Extremely wide (and pulsating) hilar shadows are also seen in cases of congenital heart disease such as interatrial septal defect, patent ductus arteriosus, in pulmonic valvular insufficiency, and occasionally in heart block.

The *lung fields* appear cloudy (Fig. 21*A*), partly because of an accentuation

and widening of the lung markings (i. e., the branches of the pulmonary vessels), and partly because of congestion, fibrosis or edema of the pulmonary tissue between the vessels.[25, 49] The dense hilar shadows radiate in a fanlike fashion toward the periphery and particularly toward the base of the lungs. Where the engorged vessels run perpendicularly to the film, they appear as conspicuous round shadows which may simulate miliary tuberculosis or carcinomatosis. There is often a diffuse haziness of the lung in its median and peripheral portions while the periphery is clear. Homogeneous mottled areas may result from alveolar exudation. Sometimes the homogeneous densities are indistinguishable from infarcts or consolidation. In pulmonary edema the shadows are usually widespread and symmetrical (Fig. 22). Chronic pulmonary stasis with fibrosis and deposition of hemosiderin produce nodular foci which may become calcified or rarely ossified.



A B

Fig. 22. *A,* Acute pulmonary edema in glomerulonephritis precipitated by intravenous infusions. Exaggerated hilar and pulmonary markings. Diffuse haziness, especially of medial portions of lung fields with clearing at periphery and bases.
B, After recovery, one week later.

Immediately after an attack of acute pulmonary edema there may be a cloudiness of the lung field in the area around the hilar shadows, while the periphery of lung fields is clear. Then the shadow due to pulmonary edema extends to the bases. The mechanism of this spread has been discussed by Zdansky.[76] Free and encapsulated pleural effusions have been noted, especially by Bedford.[3] The roentgenologic picture of pulmonary engorgement may also be complicated by the coexistence of bronchopneumonia and pulmonary infarcts.

The *cardiac silhouette* in left-sided heart failure is determined chiefly by the underlying diseases for which the appropriate chapters should be consulted. With the development of left-sided heart failure, there is evidence of progressive enlargement of the failing chambers.

Circulatory Measurements. The *circulation time* is prolonged. The arm-to-tongue time (p. 139) exceeds 16 seconds, the upper limit of normal, and may be 40 seconds or more. This is due to slowing of the blood stream in the dilated

heart and especially in the congested lungs. In the early stages of left-sided failure the arm-to-lung time (ether) (p. 140) may be normal indicating that the slowing is limited to the venous side of the pulmonary circulation. With frank left-sided failure both the arm-to-lung and arm-to-tongue time are prolonged.

The *vital capacity* is diminished.

The *venous pressure* is normal in the absence of concomitant right-sided heart failure.

The *basal metabolic rate* may be slightly or greatly elevated (+15 to +60 per cent)[60] due to excessive work of the muscles of respiration and increased oxygen consumption of the enlarged heart. In cases of pure right-sided failure due to constrictive pericarditis, in which there is no dyspnea, the basal metabolism is normal.

The *arterial blood pressure* may be unchanged, may fall or may become elevated (Hochdruckstauung[63, 19a]), depending in large measure on the underlying disease and the factors precipitating heart failure.

Diagnosis and Differential Diagnosis of Left-Sided Heart Failure

The diagnosis of left-sided heart failure is made on the basis of the characteristic symptoms and signs of pulmonary congestion in a person with the types of cardiac disease which usually underlie left-sided heart failure.

The usual symptoms of pulmonary congestion are exertional dyspnea, orthopnea, paroxysmal dyspnea (cardiac asthma), pulmonary edema, cough and hemoptysis. The chief physical signs are râles at the bases of or throughout the lungs, accentuation of the second pulmonic sound, gallop rhythm and alternation of the pulse. Many or all of these signs may be absent. Roentgen ray examination reveals an enlarged heart, prominence and widening of the hilar shadows and clouding of the lung fields. A prolonged circulation time is a valuable diagnostic confirmation.

Differential diagnosis involves most often the distinction of left heart failure from bronchopulmonary disease, as suggested by such symptoms as cough, dyspnea, hemoptysis and asthma. Roentgenograms of the chest, physical and electrocardiographic examination to determine the presence of underlying cardiac disease and a careful history provide the needed data. A prolonged circulation time distinguishes cardiac from bronchial asthma.[50] Differentiation between cardiac and bronchopulmonary dyspnea is said to be aided also by radiocardiography,[59a] a graphic recording of the passage of radioactive blood through the cardiac chambers following the intravenous injection of radioactive Na^{24}. Dyspnea must be carefully evaluated to distinguish it from psychogenic disturbances in respiration.

RIGHT-SIDED HEART FAILURE

Right-sided heart failure is most often combined with left-sided heart failure. In fact left-sided heart failure, with its associated pulmonary congestion and pulmonary hypertension, is the commonest cause of failure of the right ventricle.[68] Sometimes the entire heart fails simultaneously, but the clinical features are predominantly those of right-sided heart failure. Occasionally, however, isolated right-sided heart failure is seen without left-sided heart failure.

Causes of Right-Sided Heart Failure

The underlying cardiac diseases which cause right-sided heart failure may be grouped as follows:

1. Conditions associated with left-sided heart failure and consequent pulmonary congestion and pulmonary hypertension which place a strain on the right ventricle. Thus left-sided heart failure in essential hypertension, coronary artery disease and aortic and mitral valvular disease is followed usually in a few months or years by failure of the right ventricle.

Under the heading of Bernheim's syndrome[5] are included cases of pure right-sided heart failure due to lesions which cause massive hypertrophy of the left ventricle including the interventricular septum.[62] The latter encroaches on the right ventricular chamber to such an extent that there is a functional obstruction to inflow into the right ventricle. The syndrome is not well established as an entity. The diagnostic features are said to be enlarged liver, peripheral edema, enlargement of the left ventricle, absence of râles in the lungs or other evidence of left heart failure.

2. Conditions which impair the function of the entire myocardium but which produce a predominant picture of right-sided heart failure. When the entire heart is affected, the right ventricle being weaker than the left fails more readily and the diminished output of the failing right ventricle spares the left ventricle, e. g., rheumatic, diphtheritic or toxic (Fiedler's) myocarditis, severe anemias, beriberi and arteriovenous fistula.

3. Primary diseases of the lungs, pulmonary vessels or pulmonic valve which cause strain and consequent failure of the right ventricle (cor pulmonale) (p. 890). These instances of primary or isolated right ventricular failure are rare as compared with the cases of isolated left ventricular failure.

4. Rare cases of predominant or isolated tricuspid stenosis cause failure of the right atrium and a clinical picture identical with that of right ventricular failure except for the signs of the primary disease.

5. Conditions causing an obstruction to the inflow of blood into the right atrium such as constrictive pericarditis. The resulting systemic venous engorgement produces a clinical picture like that with tricuspid stenosis in which there is a similar obstruction to inflow. Prolonged ectopic tachycardias may also lead to right-sided heart failure.

Pathologic Physiology of Right-Sided Heart Failure

This is discussed in detail in Chapter 6. Briefly, the pulmonary congestion of left-sided heart failure or of primary pulmonary disease leads to hypertension of the pulmonary artery. The increased resistance to pulmonary outflow is compensated by right ventricular dilatation and hypertrophy. Eventually this compensation is inadequate and the right ventricle is unable to maintain an adequate output.

Extracardiac compensations, especially renal retention of sodium and water, augment the circulating blood volume and venous return to the right atrium and ventricle. The incompetent right heart is unable to accept and expel this venous return, and blood is dammed up in the systemic veins and capillaries. This series of events is characterized by increased circulating blood and a progressive rise in pressure in the pulmonary artery, right ven-

tricle, right atrium, central and peripheral veins and in the capillaries of the skin and viscera.[6]

The symptoms of right-sided heart failure are largely due to engorgement and elevation in pressure of the systemic veins and capillaries and the associated sodium-water retention.

Pathology of Right-Sided Heart Failure

Liver. The liver is dark red or brownish, enlarged and firm because of chronic passive congestion.[40] In cases of longstanding congestion it may undergo subsequent atrophy so that it is only slightly enlarged or even smaller than normal.[8] The term "nutmeg" liver refers to the appearance produced by the alternation of dark red and light brown areas. The former is due to the central areas of venous congestion, the latter to lesser congestion and the deposition of fat in the periphery of the lobule. Eventually extensive fibrosis leads to *cyanotic induration,* while subsequent necrosis and atrophy cause *cyanotic atrophy* of the liver. When the process of connective tissue replacement and fibrous retraction is extensive, the changes in the liver are described as cardiac cirrhosis.[33, 21, 37] Sclerosis of the hepatic veins[47] and of the superior vena cava[26] has been described, due presumably to the elevated pressure in these vessels during right-sided heart failure. The incidence of cardiac cirrhosis of the liver varies between 0.7 and 5 per cent of cases of heart failure, depending on the criteria employed by different observers. Cardiac cirrhosis is most apt to occur with multiple attacks of heart failure and especially when there is a very high hepatic venous pressure of prolonged duration. I have observed it most often with constrictive pericarditis and with tricuspid valvular disease. The factor of an independent Laennec's cirrhosis is sometimes difficult to exclude.

Peritoneal Cavity, Gastrointestinal Tract, Spleen and Pancreas. Elevation of pressure in the peritoneal capillaries is the chief factor leading to the transudation of fluid and the appearance of variable and sometimes vast quantities of ascitic fluid in the peritoneal cavity. Secondary infection of the ascitic fluid may cause inflammation and thickening of the peritoneum and of the peritoneal covering of the viscera, especially the liver. The hypertension of the portal circulation also causes passive congestion in the veins and capillaries of the entire gastrointestinal tract, with consequent edema, thickening and occasionally hemorrhages.

The *spleen* is enlarged, dark red and firm (cyanotic induration), as a result of passive congestion of the portal (and hence of the splenic) circulation. According to Fowler[18] the spleen was sufficiently large to be theoretically palpable (i. e., over 300 gm.) in 13.4 per cent of 97 cases of uncomplicated congestive heart failure. The *pancreas* may also be the site of passive congestion.

The Kidney. The kidney appears dark red and is firmer than usual, because of chronic venous congestion. The essential microscopic feature is the widening and engorgement of the intertubular veins and capillaries and usually also of the glomerular capillaries. There is some proliferation of intertubular connective tissue but heart failure does not lead to significant fibrosis or contraction of the kidney.

The Brain. Venous congestion with and without edema of the brain and leptomeninges, and alterations of the ganglion cells and nerve fibers, have been described. But the many cerebral symptoms seen in advanced heart failure are

more probably due to severe cerebral arteriosclerosis, sometimes with infarcts and encephalomalacia, or to cerebral emboli, arising in left atrial or ventricular thrombi.

Clinical Picture of Right-Sided Heart Failure

Although the clinical pictures of right- and left-sided heart failure are sharply segregated for purposes of presentation and to emphasize their occurrence as isolated syndromes, it must be remembered that the symptoms of left- and right-sided heart failure are usually combined sooner or later, and often they appear almost simultaneously.[10, 1a]

Symptoms and Signs of Right-Sided Heart Failure. *The Heart and Lungs.* In the usual case of right-sided heart failure, the left heart is also insufficient and the signs in the heart and lungs are essentially those described under left-sided heart failure (p. 65).

Cardiac enlargement is more pronounced and more universal than in pure left heart failure. Roentgenograms may disclose definite enlargement of the right ventricle and atrium. The shadows of the superior and inferior venae cavae become more distinctive. The entire cardiac silhouette becomes enlarged to the left and right, encroaching on both pulmonary fields and somewhat obliterating the individual cardiac contours. There are insufficient comparative studies of the size of the heart, but a few series indicate that the cardiac silhouette often undergoes distinct enlargement with failure, and a diminution in size following recovery.[53] Comparisons are often difficult because of differences in technic and changes in the position of the diaphragm at the respective examinations during failure and in its absence.

In cases of pure right-sided heart failure secondary to intrinsic pulmonary disease, enlargement of the heart is often difficult to demonstrate. There may be an enlargement only in the anteroposterior diameter or enlargement of the right chambers may be demonstrable in oblique views (p. 29).

In combined right and left heart failure, râles at the pulmonary bases persist. Hydrothorax occurs commonly, especially on the right side or bilaterally. Clouding of the medial and lower lung fields is frequently observed on roentgenologic examination. Pulmonary infarction is common and may be associated with pleural effusion. In cases of pure right-sided heart failure due to pulmonary disease, the roentgenologic findings in the lungs are those of the underlying pulmonary disease. In cases of tricuspid stenosis and constrictive pericarditis with failure, the pulmonary fields are often remarkably clear but hydrothorax is frequent.

The *electrocardiogram* is not characteristic and is determined by the underlying disease or by complicating arrhythmias, especially auricular fibrillation. Prolongation of the QT interval is usual.[12]

Subcutaneous Edema. Edema, or the demonstrable accumulation of excessive fluid in the subcutaneous tissues, is a classic feature of right-sided heart failure. Usually it appears in a cardiac patient who has been suffering for months or years from dyspnea on exertion, orthopnea or cardiac asthma. Occasionally a patient with heart disease who has never noted any of the above symptoms begins to complain of swelling of the feet or ankles, which usually appears in the evening and subsides after a night's rest in bed. A considerable amount of fluid may accumulate in the subcutaneous tissues before edema

becomes apparent (invisible edema). This may be noted as an increase in body weight. Conversely, the loss of invisible edema fluid may cause a reduction in weight and a continued diuresis after all visible edema has disappeared.

The edema may occur in any part of the body, but because its formation is determined chiefly by an elevated hydrostatic capillary pressure, it is usually found in dependent parts of the body such as the feet, ankles (especially the inner malleoli), and pretibial region. In a patient who has been in bed for some days or longer, the edema is most prominent over the sacral region and may be overlooked unless this part of the body, which is now the most dependent, is carefully examined. In patients with hemiplegia the edema is most conspicuous on the paralyzed side.[52] Sometimes there is generalized, massive edema (anasarca) affecting all parts of the body including the genitalia, chest wall, arms and, rarely, the face. In the primary forms of right ventricular failure, in which orthopnea is usually absent and the patient sleeps in the recumbent position, there may be edema of the face or eyelids on arising. But as a rule, edema of the face should suggest a renal etiology or some obstruction of the superior vena cava.

Ascites. Ascites, or effusion of serous fluid into the abdominal cavity, is the result of engorgement in the portal venous tributaries. As a rule it is a later development and a less prominent feature than subcutaneous edema, but in some forms of right-sided heart failure (with tricuspid stenosis or constrictive pericarditis) there is considerable ascites with little edema.

The ascites may cause no subjective symptoms or the patient may notice only an increase in his abdominal girth. Sometimes it leads to abdominal distention and distress or even to abdominal pain. The ascites is often persistent and may recur repeatedly after aspiration. In cases of constrictive pericarditis persistent and recurrent ascites is a characteristic feature.

Hydrothorax and Hydropericardium. Subcutaneous edema and ascites are often associated with effusions into the pleural cavity (hydrothorax) (Fig. 21*B*) and sometimes into the pericardial cavity (hydropericardium) to form the complete picture of cardiac dropsy. Hydrothorax has been mentioned as occurring in left-sided heart failure (p. 68), as well as in right-sided heart failure, since the pleura drains into the pulmonary as well as into the systemic veins. The pleural effusions in right-sided heart failure occur most often in the right pleural cavity or are most extensive on that side when there are bilateral effusions. In left-sided heart failure with regular rhythm the effusions, according to Bedford and Lovibond,[4] are usually on the left side but this has been questioned.[44]

Pathogenesis of Hydrothorax (see p. 121).

Usually pleural effusions are absorbed as heart failure improves but interlobar effusions are sometimes persistent. The chief effect of hydrothorax is to produce dyspnea or more often to exacerbate the dyspnea present by compressing the lung, by diminishing its vital capacity and by reflex stimulation of breathing.

Engorgement of Superficial Veins. The large cervical veins and those on the dorsum of the hand may appear full and prominent. In cases of advanced heart failure there may be pulsations of the superficial veins of the extremities.[34] The retinal[30] and lingual veins[43] may also be conspicuously engorged with right-sided heart failure.

The normal pulsations of the cervical veins are best seen over the jugular bulb in the root of the neck with the patient supine. In cases of right-sided

heart failure the veins may become too distended to pulsate when the patient is supine. As his head is gradually elevated, a point of intense venous pulsation is reached. Normally the cervical veins appear empty when a person is erect; with severe right-sided heart failure these veins appear extremely engorged and their pulsations may be prominent. The ventricular form of venous pulse (p. 620) may be seen if there is associated auricular fibrillation or tricuspid insufficiency.

Prominence of the superficial veins is an early sign of right-sided heart failure and may be noticeable before there is detectable subcutaneous edema, hepatic enlargement or other signs of heart failure. This sign may persist even after rest in bed, diuretics and other therapeutic measures have eliminated the edema. Occasionally engorgement of the superficial cervical veins is revealed only by pressure over the right upper quadrant of the abdomen (hepato-jugular reflux). It is important to remember that in right-sided heart failure engorgement occurs in the tributaries of both the superior and inferior venae cavae. When venous congestion is limited to the upper or lower portions of the body, some local venous obstruction should be sought.

Enlargement and Tenderness of the Liver. The enlarged liver can almost invariably be palpated clinically. Its lower border may extend to the level of the umbilicus. Hepatic enlargement is often present long before there is edema. The liver often remains enlarged when all other symptoms of right-sided heart failure have disappeared. Often there is abdominal tenderness in the hepatic region, due presumably to tension of the liver capsule. With severe heart failure, especially if there is significant tricuspid valvular insufficiency or auricular fibrillation, the liver pulsates synchronous with the right ventricular pulsations (see p. 621).

The large liver may not only be tender on pressure but may cause spontaneous abdominal pain. The abdominal pain rarely simulates that of cholelithiasis or cholecystitis. Mild abdominal pain in patients with congestive heart failure may also be due to intense distention resulting from gastrointestinal disturbances (p. 76) or ascites.

Abdominal pressure over the engorged liver causes or increases visible engorgement of the cervical veins and a rise in venous pressure. This phenomenon, known as the hepato-jugular reflux, is a diagnostic sign of right-sided heart failure and helps differentiate hepatic enlargement due to venous engorgement from that due to other conditions. Hepatic compression increases the venous return and intensifies the stasis in the cervical veins, due to the inability of the failing right heart to handle the increased blood flow.

Liver Function and Jaundice. Hepatic congestion is often associated with a disturbance in the function of the liver.[11a, 11b] Urobilinogen in the urine is increased. Hyperbilirubinemia is frequently present with right-sided heart failure, while frank jaundice occurs in 2 to 5 per cent of the cases.[39] The patients with jaundice usually suffer from combined left- and right-sided heart failure and have pulmonary infarcts as well as an engorged liver. In edematous areas the skin may not be jaundiced because the bile pigments do not enter into the edema fluid[45] or only to a slight extent,[1] possibly because of its low content of protein. Jolliffe[32] found impairment of hepatic function indicated by excessive retention of injected bromsulfalein in 12 of 16 patients with right-sided heart failure. However, the levulose tolerance test revealed hepatic damage in only three of the cases. The van den Bergh reaction is often delayed or

indirect, but occasionally a prompt direct reaction is observed. There is some uncertainty whether the abnormal bromsulfalein test in cases of congestive heart failure actually denotes hepatic damage or is due entirely to circulatory stasis.[5a, 6a]

Pathogenesis of Jaundice in Heart Failure (p. 125).

Cyanosis. A bluish discoloration of the skin and mucous membranes due to an excessive concentration of reduced hemoglobin in the blood is almost always seen in patients with right-sided heart failure. It occurs most often and is most intense in the cases in which heart failure is secondary to pulmonary diseases or to congenital cardiac lesions causing a considerable admixture of arterial and venous blood. When right-sided heart failure complicates left-sided heart failure, dyspnea may be alleviated but cyanosis appears or becomes intensified. In left-sided heart failure the severity of dyspnea is usually out of proportion to the cyanosis; in right-sided heart failure due to pulmonary lesions the cyanosis is often more prominent than the dyspnea. In most cases of combined right-sided and left-sided heart failure both dyspnea and cyanosis are prominent manifestations.

Pathogenesis of Cyanosis (p. 123).

General Symptoms. Fever usually denotes associated pulmonary infarction or bronchopneumonia, or it may be due to rheumatic activity, bacterial endocarditis or some other infection.

Weakness may be a prominent symptom in advanced failure, and is sometimes associated with extreme loss of weight and anemia (cardiac cachexia). Most frequently it is the result of excessive sodium restriction combined with the vigorous use of mercurial diuretics.

Gastrointestinal Disturbances. Due to venous engorgement anorexia and abdominal distention or a sense of fullness after meals are frequent. Many gastrointestinal symptoms, especially anorexia, nausea and vomiting, may occur not because of passive congestion but because of digitalis, morphine or other drugs. The combination of meteorism with hepatic enlargement (and sometimes also ascites) may cause intense abdominal tension or even pain. Constipation is sometimes distressing; more rarely there is diarrhea. Intestinal bleeding is occasionally observed.

Renal Symptoms. Nocturia occurs frequently and may be due to an associated prostatic enlargement, to the elimination of occult edema fluid when the patient is recumbent, or to irritation of the bladder or urethra by concentrated urine. Temporary anuria may follow active diuresis.

Oliguria is a characteristic feature of right-sided heart failure. Since the diminution in urinary output parallels the severity of the heart failure, the urinary volume is usually a good index of progress. When improvement occurs, the volume increases; with spontaneous or therapeutic diuresis a polyuria of 2.5 to 4 liters daily may appear.

The *urine* is concentrated and has a *high specific gravity,* usually between 1.025 and 1.030. However its sodium content is minimal.[11, 19] When cardiac edema disappears as a result of spontaneous or therapeutic diuresis, the specific gravity may be very low but the content of sodium and chlorides is increased. The specific gravity of the urine may also remain low if cardiac failure complicates renal insufficiency or following frequent mercurial diuretics, or prolonged and extreme restriction of sodium intake.

Albuminuria is a common occurrence with congestive heart failure. Usually

the albuminuria is slight, the concentration being less than 1 per cent and the daily excretion of albumin less than 1 gram. Hyaline casts and sometimes granular and epithelial casts accompany the albuminuria. Renal function, as determined by urea clearance and PSP tests, is usually depressed.[8a] (See also p. 83.)

The *chemistry of the blood* may be altered. Moderate *azotemia* (urea nitrogen between 20 and 40 mg. per 100 cc. blood) has been noted when there is severe oliguria. Vigorous mercurial diuresis may result in increasing azotemia despite a large urinary output.[19] Occasionally there is *hypoproteinemia,* the reduction being confined essentially to serum albumin. Hypoproteinemia is most likely to occur after prolonged cardiac failure as a result of malnutrition, impaired hepatic formation of albumin, and perhaps also of a long-continued loss of albumin in the urine and in serous effusions.

BLOOD ELECTROLYTES. The *concentration of sodium* in the plasma is usually diminished despite the reduction in urinary sodium.[18a] This is only partly due to dilution by an increased plasma volume. Indirect evidence suggests that the reduction in plasma sodium may be due in part also to the passage of significant amounts of this ion into the cells.[18a] A prolonged, extremely low sodium intake and desalting with frequent mercurial diuretics may also produce hyponatremia. On the other hand, recovery from heart failure is associated with a restoration of plasma sodium to normal concentration.

In general plasma chlorides behave like sodium. Like the latter chlorides are poorly excreted in the urine, but there is often a quantitative dissociation. We have often observed that the plasma chloride concentration is relatively normal when the plasma sodium is depressed.[18a] In such instances there is usually a low carbon dioxide combining power and a tendency to acidosis. On the other hand, the plasma chloride may be much more depressed than the sodium, with a concomitant elevation in carbon dioxide and a tendency to alkalosis. The latter findings occur following prolonged, drastic mercurial diuresis in patients with a very low sodium intake. In the presence of intrinsic renal disease both plasma sodium and chloride are diminished in concentration, but there is evidence of acidosis due to retention of fixed acids.

The *plasma potassium* is relatively normal, but balance studies during recovery from heart failure[65a] and studies of potassium excretion following diuretics[18a] suggest that this essentially intracellular ion may undergo significant shifts out of the cell.

Disturbances of the Nervous System. Aphasia, paralyses, convulsions and coma may be due to a complicating cerebral embolism with infarction and encephalomalacia. The embolism arises from a thrombus in the left auricular appendage in cases of mitral stenosis and auricular fibrillation or on the wall of the left ventricle over the site of infarction or aneurysm. Rarely syncope or convulsions may accompany cardiac asthma or pulmonary edema due to left ventricular failure.

There are numerous neurasthenic, neurotic or psychotic manifestations which may or may not be directly related to the cardiac failure and its associated passive venous congestion. Headache is a common symptom. Insomnia and bad dreams or nightmares are sometimes very distressing. Hypochrondriasis and depression may be due to the patient's knowledge that he is suffering from heart disease or heart failure. Occasionally there are true psychoses with disorientation, delirium, hallucinations and delusions, especially of a paranoid

type.[23] Psychotic symptoms as well as pronounced weakness may follow extreme diuresis after mercurial drugs. This may be due to dehydration and loss of sodium chloride. Morphine and barbiturates are frequently contributory causes of mental symptoms. Psychotic symptoms may be due also to digitalis intoxication. In most cases of heart failure, mental symptoms are absent.

Circulatory Measurements. The *circulation time is prolonged.*

The *blood volume* is augmented.[22, 46]

The *venous pressure* is elevated in contrast with the normal venous pressure of pure left-sided heart failure.

The *cerebrospinal fluid pressure* is determined by the venous pressure and is elevated in cases of right-sided heart failure.

The *arterial blood pressure* undergoes no characteristic change.

Diagnosis of Right-Sided Heart Failure

The diagnosis of right-sided heart failure is usually simple in patients with known cardiac disease or with preceding left-sided heart failure. The combination of congested cervical and peripheral veins, subcutaneous edema of the dependent parts, and hepatic enlargement usually suffices to make the diagnosis. An elevation of venous pressure with or without pressure over the right upper quadrant of the abdomen is confirmatory. In incipient right-sided heart failure the venous pressure may not be elevated. However, the tendency to systemic congestion may be demonstrated by the hepato-jugular reflux or by a rise in venous pressure following the intravenous infusion of 1500 cc. of isotonic saline in thirty minutes.[61] Normally there is no rise in venous pressure. However the latter procedure is a dangerous one and should not be used as a clinical test.

I have often seen middle-aged and usually obese women who complain of shortness of breath and swelling of the ankles, because of which they were told their hearts were failing. Study usually revealed that the dyspnea was due to lack of exercise and obesity or that it was merely a psychogenic inability "to take a full breath" or a tendency to sighing respiration. The edema was usually hypostatic, due to flat feet, varicose veins, obesity and prolonged standing. That these individuals are not suffering from heart failure can be proven by the exclusion of underlying hypertension or heart disease, with roentgen ray examination of the chest and electrocardiography, and by the finding of a normal venous pressure and normal circulation time.

Differential diagnosis involves the differentiation between heart failure and the multiplicity of pulmonary, renal, hematologic, hepatic and abdominal or thoracic diseases which may produce dyspnea, edema, venous engorgement, cough, hepatic enlargement, hydrothorax or pleural effusion or ascites. If heart failure is present it should be possible to demonstrate some underlying causative cardiovascular disease. Cardiac enlargement should be demonstrable except with constrictive pericarditis. If the right heart has failed, the physician should demonstrate that the venous engorgement and elevation of venous pressure concern both the superior and inferior caval systems and not merely one or the other. A prolonged circulation time is diagnostic of heart failure in the absence of polycythemia vera. On the other hand, fever, severe anemia, hyperthyroidism, beriberi, severe emphysema and arteriovenous aneurysm tend to restore the prolonged circulation time of heart failure to within the normal range.

COURSE AND PROGNOSIS OF CONGESTIVE HEART FAILURE

The course and cause of death in congestive heart failure are often determined or modified by the underlying cardiac disease. Death is often precipitated by a pulmonary or cerebral embolism and infarction or by an acute coronary occlusion. Acute pulmonary edema is a frequent form of termination. In their analysis of the causes of death in 185 patients with congestive heart failure, Williams and Rainey[72] emphasized the relative increase in importance of fatal pneumonias. Since their study, the liberal use of sulfonamides and antibiotics has sharply reduced the incidence of fatal pneumonia. Uremia is fairly common as a cause of death in patients with malignant hypertension or nephritis and heart failure.

Left-sided heart failure is often variable in its course and duration. I have known cardiac patients who have suffered from exertional dyspnea and slight orthopnea for ten or more years before the symptoms of right-sided heart failure developed. In patients with mitral stenosis mild symptoms of pulmonary congestion are almost part of the disease itself, for they occur early and may last many years before the patient is unable to carry on his normal activities. However, in the presence of dyspnea on slight exertion or at rest, repeated attacks of cardiac asthma, recurrent pulmonary edema, alternation of the pulse or persistent gallop rhythm, the outlook is usually unfavorable and life lasts from six months to two years at the most.

Most of the studies on prognosis in heart failure state that the duration of life in cardiac disease complicated by right heart failure is only one to two years and rarely up to five. Grant[24] found the average duration of life in the presence of venous congestion was two and a half years. Williams and Rainey[72] found that in the period between 1931 and 1935 patients hospitalized with congestive heart failure due to rheumatic heart disease lived 32 months, those with arteriosclerotic heart disease 40 months and those with luetic heart disease 11 months. But in recent years I have seen many patients who have survived five to ten years after the development of right-sided heart failure. This is undoubtedly due to judicious restriction of sodium and administration of mercurial diuretics in the past twenty years.

In general the outlook is relatively favorable if the symptoms of congestive failure subside rapidly and completely with appropriate treatment. The less intense and prolonged the required treatment before recovery is effected the more probable is the persistence of recovery.

An important clue as to the patient's course is obtained from a study of his renal excretion of sodium and his response to the ingestion of moderate amounts of sodium chloride.[19] Some patients excrete sodium fairly well after disappearance of their symptoms of heart failure, and there is no recurrence of symptoms or evidence of water retention following the daily ingestion of 5 to 10 gm. of sodium chloride for five days. As a rule, heart failure in these patients was induced by an infection, a pulmonary infarct, anemia or some other factor which subsided or was eliminated by treatment. These patients have a relatively good immediate prognosis and their hearts remain compensated with little or no sodium restriction and without the use of mercurial diuretics.

At the other extreme is a host of patients who, even after vigorous treatment and control of overt symptoms, excrete almost no sodium in the urine and promptly experience a retention of fluid and recurrence of symptoms follow-

ing the ingestion of 5 to 10 gm. of sodium chloride daily for five days. Heart failure in these patients can only be controlled by extreme sodium restriction and the frequent administration of mercurial diuretics in addition to other therapeutic measures. Other patients fall between these two extremes; their outlook for maintenance of clinical improvement may be graded according to their renal excretion of sodium and their response to the ingestion of sodium chloride.

The outlook is relatively better if there is an obvious precipitating factor which can be eliminated, than if congestive heart failure appears without any apparent immediate cause or as a result of one which cannot be treated. Sodeman and Burch[66] found that of 47 patients in whom congestive heart failure appeared gradually and without apparent precipitating cause 46 were unable, in spite of treatment, to compensate sufficiently to carry on minimal normal activity. On the other hand, in 54 patients with a demonstrable precipitating cause for congestive heart failure, compensation was established rapidly under treatment so that the patient could resume his activities.

The outlook is also relatively better in the well-to-do than in persons of low economic level. Cooperation and intelligent execution of the physician's orders by the patient and his family also improve the outlook. The prognosis in any given case of congestive heart failure should be guarded even when it appears relatively favorable, because of the danger of serious complications or sudden death.

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6

THE PATHOGENESIS OF CONGESTIVE HEART FAILURE

Congestive heart failure denotes prolonged impairment of the ability of the heart to maintain an adequate blood flow to the tissues. The manner in which such disability arises was discussed in the chapter on the etiology of heart failure. We are concerned here with the mechanism by which such cardiac impairment leads to the *manifestations* of congestive heart failure. Two main concepts have been advocated: the so-called "forward-failure" and "backward-failure" theories. They deserve presentation because they crystallize our understanding of the problem and the points which remain to be clarified.

THE FORWARD-FAILURE THEORY

According to the "forward-failure" hypothesis,[30, 29] the symptoms of congestive heart failure arise primarily because of the heart's continued inability to pump enough blood to meet the demands of the tissues. The term *forward* denotes that the inadequate blood supply is due to an actual diminution of blood propelled in a forward direction from the heart. This is in contrast with the "backward-failure" theory which postulates that the symptoms of heart failure are caused, not by a diminished forward (arterial) output of blood from the heart, but by a backward damming of blood into the great veins and their venocapillary tributaries in the various tissues and organs.

Forward Failure and Inadequate Cardiac Output

The fundamental assumption of the forward-failure theory is that there is an inadequate cardiac output. Formerly, symptoms and signs in each individual organ were interpreted as the direct consequence of the insufficient blood flow to that organ.[25] In its more recent form, symptoms of congestive heart failure are attributed only in part to a direct consequence of inadequate blood flow to individual organs, and in part to a retention of sodium and water throughout the tissues because of insufficient blood flow to the kidneys. Less emphasis is placed on an absolute diminution in cardiac output than on the deficiency of cardiac output relative to the requirements of the tissues.[55, 9] Therefore the output may be adequate at rest but inadequate during activity when symptoms of failure appear. In certain conditions such as hyperthyroidism, anemia, beriberi, etc., heart failure may be present even when the cardiac output exceeds

basal normal values because the output is still less than is required under the given abnormal conditions. In the presence of advanced heart failure, symptoms such as weakness and fatigability, believed to result directly from inadequate blood flow (to the muscles), are masked by dyspnea, orthopnea and edema, believed to result indirectly from impaired renal excretion of sodium and water. When the latter symptoms are alleviated by the restriction of sodium and by the administration of mercurial diuretics, weakness and fatigability become more apparent.

Forward Failure and Sodium-Water Retention by the Kidneys

The belief that the major phenomena of congestive heart failure are due to sodium and water retention resulting from inadequate cardiac output and consequent renal impairment is based on the following:

1. Impaired Sodium Excretion. Patients with persistent or recent heart failure suffer from an impaired ability to excrete sodium. Futcher and Schroeder[12] injected 400 cc. of 6 per cent sodium chloride solution intravenously over a period of thirty minutes in patients convalescing from congestive heart failure. The renal excretion of sodium and chloride in the next twenty-four hours in the patients with severe heart disease was not more than 30 per cent of that observed in normal controls. Similarly Proger et al.[41] administered excessive amounts of sodium chloride by mouth to patients recently recovered from heart failure and observed an abnormal retention of sodium concomitant with the recurrence of their symptoms. Tracer studies with radiosodium (Na^{24} and Na^{22}) have shown delayed excretion and retarded turnover of sodium during heart failure.[6, 61a]

2. Diminished Renal Blood Flow. Impaired renal excretion of sodium during heart failure has been related to a diminished cardiac output and consequent reduction in renal blood flow. Merrill[32] found by the direct Fick method that patients with congestive heart failure usually have a diminished cardiac output. The renal blood flow in these patients, as determined by the para-amino hippurate method, was reduced to one third to one fifth of normal, and in general bore a high degree of correlation with the diminished cardiac output. Since the reduction of renal blood flow was greater than the reduction of cardiac output, there appeared to be a specific diversion of blood away from the kidney. Because the diminished renal blood flow was related to the diminished cardiac output but bore no relation to the venous pressure, the findings were interpreted to support "the forward-failure" and not the "backward-failure" theory. Similar findings were reported by Mokotoff, Ross and Leiter.[35]

3. Sodium Balance and Clinical Features. Clinical and experimental observations have indicated that relief or recurrence of dyspnea, edema and other phenomena of heart failure is closely related to the intake and retention of sodium. The rapid intravenous infusion of sodium-containing fluids or the oral ingestion of large amounts of sodium by patients with heart disease or recent heart failure is frequently followed by a clinical picture identical with that known as congestive heart failure.[12, 41, 43, 63]

Similarly, striking relief of symptoms and signs of heart failure has been effected by keeping the sodium intake extremely low.[47, 45, 23, 5, 14] As long as the sodium intake is sharply restricted, fluids can be taken freely without harm; according to Schemm,[45] forced fluid intake actually promoted diuresis.

These observations have been interpreted as denoting the primary importance of sodium balance in producing symptoms of heart failure and as minimizing the effects of backward-failure with its increase in venocapillary pressure.

4. Relative Importance of Sodium Retention and Elevated Venous Pressure. Observations by Warren and Stead[63] on the appearance of heart failure were interpreted to indicate that salt and water retention in the body tissues precedes the development of an elevated venous pressure. They administered 9 to 12 gm. of sodium chloride by mouth to patients recently recovered from congestive heart failure and made daily observations of weight and frequent observations of the venous pressure. A significant weight gain, presumably due to salt-water retention, occurred when the venous pressure was still normal; elevation of venous pressure occurred a few days later. (See discussion, p. 100.)

THE BACKWARD-FAILURE THEORY

The backward-failure theory maintains that the *clinical manifestations of congestive heart failure* are due to passive engorgement of the venous system and tributaries caused by a backward rise in pressure upstream from (i. e., proximal to) the failing cardiac chambers.[17] It differs fundamentally from the theory of forward-failure in denying, not that there may be a reduction in the cardiac output, but that the symptoms of congestive heart failure are directly due to this reduction. Suggested first by Vieussens[62] in 1715, the backward-failure hypothesis was accepted by Corvisart,[8] who wrote the first French treatise, and by Hope,[20] who wrote the first English textbook on heart disease. According to these authors the cardinal symptoms of heart failure were due to passive venous engorgement of blood in the affected organs behind the failing heart.

The backward-failure theory is based on:

1. Experimental studies of the circulation.
2. Pathologic anatomic observations in cases of congestive heart failure.
3. Clinical observations on patients with compensated and decompensated heart disease.

Correlation of Experimental Circulatory Studies with Backward-Failure Theory

The studies of Starling,[51] Straub[57] and others on the heart-lung preparation and with similar experimental circulatory set-ups showed that the important cardiac and circulatory disturbances occurred *behind* the experimental obstruction or lesion, while the abnormalities in front of or downstream from the lesion were only temporary and rapidly compensated (Chapter 1). Thus when the outflow from a cardiac chamber is obstructed, or when the heart begins to fail, the cardiac output is only slightly and temporarily diminished. The affected chamber dilates, contracts more forcefully because of the consequent lengthening of the cardiac fibers, and thereby restores the normal output. The venous pressure remains normal. This corresponds to the clinical state of compensated heart disease.

With increasing fatigue of the heart, the pressure within the cardiac chambers becomes so elevated that the venous return to the heart is embarrassed. Now the venous pressure rises, i. e., backward from the heart. This corresponds to the clinical stage of congestive heart failure. With fatigue of the chambers on

the left side of the heart as with experimental aortic and mitral vaivular lesions there is an increased resistance to inflow into the left atrium. The venous pressure rises in the pulmonary veins and their tributaries in the lungs. This corresponds to left-sided heart failure. With severe experimental mitral stenosis there is a rise of pressure in the pulmonary artery. This places a strain on the right ventricle. Its intraventricular pressure rises to overcome pulmonary arterial resistance. Eventually this rising pressure is transmitted backward until the venous pressure in the venae cavae and their tributaries is elevated. This corresponds to right-sided heart failure.

The increased venous pressure, according to Starling,[51] promotes cardiac filling by maintaining a pressure difference between the great veins and the auricles. This rise in venous pressure serves as a compensatory mechanism by which the cardiac output is maintained at relatively normal or slightly diminished levels. These and similar observations with individual experimental valvular lesions were interpreted to indicate that the sequence from earliest cardiac fatigue to frank heart failure is characterized by a rising pressure in the cardiac chambers retrograde from the site of disturbance into the venous system. Recent determinations, by intracardiac catheterization, of the venous pressure and of the pressures within the cardiac chambers of patients with heart failure, have confirmed these pressure changes as postulated by the backward-failure theory. For in left-sided heart failure there is a pronounced elevation in right ventricular systolic and pulse pressure, and in pulmonary arterial pressure; in right-sided heart failure there is also an elevation of the right ventricular diastolic pressure, the right atrial and the peripheral venous pressure.[3, 1b]

Pathologic Support for the Backward-Failure Hypothesis

Pathologists have long been the most ardent advocates of the backward-failure hypothesis, chiefly because of two observations:

(a) The anatomic changes in cases of congestive heart failure are characterized by passive venous engorgement and not by a deficiency of blood as would be anticipated by the forward-failure hypothesis. As an example we may consider the liver, the enlargement of which is a cardinal feature of congestive heart failure. This enlargement is seen to be due to an inordinate engorgement of blood which is confined essentially to the central veins and their capillaries.

(b) The passive venous congestion is localized in those organs which are behind (upstream from) the failing cardiac chamber. In other words venous congestion appears to result from back pressure from the failing chambers into the veins which empty into them. Thus in certain cardiac diseases the predominant strain is on the right ventricle, which eventually fails. In such instances (right ventricular failure) the venous congestion is confined to the organs which would suffer back pressure from the right side of the heart, viz., the liver, spleen, intestines, kidneys, skin, etc. In other cardiac diseases it is the left ventricle which undergoes excessive strain and fails. In cases of this type, only or predominantly the lungs show the evidences of venous congestion, as would be expected if there were back pressure from the failing left chambers. That these pathologic observations are definitely related to the clinical symptoms is seen from the fact that the symptoms caused by right-sided heart

failure are those due to venous congestion of the systemic viscera while those caused by left-sided heart failure are due to congestion of the lungs (see Chapter 7).

Clinical Observations Supporting the Backward-Failure Hypothesis

Advocates of the backward-failure theory stress its ability to account for the development of the clinical phenomena of congestive heart failure.

Left- and Right-Sided Heart Failure. Clinical observations disclose that left-sided and right-sided heart failure may occur as independent, isolated syndromes. The left ventricle fails in conditions such as hypertension, aortic valvular disease and arteriosclerotic heart disease, which put a mechanical strain on that chamber or impair its blood supply. But the symptoms of left ventricular failure, such as dyspnea, orthopnea, etc., arise in the lungs, which are in *back* of the defaulting chamber. Similarly, the symptoms of right ventricular failure such as venous engorgement, hepatic enlargement and subcutaneous edema are readily explained by back pressure from the failing ventricle into the systemic veins and capillaries. Thus the occurrence of isolated left-sided and right-sided heart failure and the group of symptoms observed in these individual syndromes support the backward-failure hypothesis.

Application of Backward-Failure Hypothesis to Individual Symptoms. The individual cardinal manifestations of congestive heart failure appear to be satisfactorily explained by the backward-failure hypothesis. Dyspnea or breathlessness is usually the earliest symptom of congestive heart failure and occurs particularly in the forms of heart disease (hypertension, aortic valvular disease, mitral stenosis) which lead to failure of the left side of the heart. The backward-failure hypothesis assumes that the dyspnea is caused by back pressure from the left side of the heart into the pulmonary veins with consequent pulmonary congestion.

That pulmonary congestion is actually present in such cases was shown by Hamilton et al.,[16] who found that the intrathoracic blood volume was twice as large as in normal individuals. Dyspnea results from pulmonary congestion which reduces the vital capacity by making the pulmonary tissue more rigid and by encroaching on the available area for ventilation. Peabody and Wentworth[38] and Harrison and his co-workers[18] actually found a diminished vital capacity in patients with congestive heart failure. Furthermore the intensity of dyspnea in such patients, while irregularly related to the cardiac output, runs closely parallel to the degree of reduction of the vital capacity.

A rise in pressure in the superficial (systemic) veins is not observed in cases of left-sided heart failure, because the back pressure extends only to the pulmonary circulation. However, when the right ventricle fails and the back pressure affects the systemic veins behind this chamber, the superficial veins are strikingly engorged and their venous pressure elevated. By similar logic, subcutaneous edema is not to be expected in isolated left-sided heart failure according to the backward-failure hypothesis. But in cases of right-sided heart failure, in which subcutaneous edema is a cardinal feature, the above-mentioned rise in venous pressure extends backward to cause a rise in intracapillary pressure. When this is sufficiently high, there is a transudation of fluid into the subcutaneous tissues. (For details, see p. 118.) Ascites occurs as a result of back pressure into the portal circulation. Other symptoms may be similarly explained by back pressure and congestion of individual viscera.

Backward-Failure Hypothesis and Sequence of Development of Symptoms. The order in which the individual symptoms and signs of congestive heart failure appear also supports the backward-failure hypothesis. Thus in cases of mitral stenosis, in which the initial strain is on the left atrium, enlargement of that chamber is followed by breathlessness which may be attributed to pulmonary congestion. Only much later do the right ventricle and atrium enlarge and fail. Subsequently, symptoms such as venous engorgement, hepatic enlargement and edema are explained by increased congestion and pressure in the systemic veins. This sequence of development of clinical features corresponds to a backward progression of rising pressure behind (proximal to) the failing chamber. A similar explanation may be presented for initial failure of the left ventricle, the right ventricle or right atrium.

THE CARDIAC OUTPUT IN CONGESTIVE HEART FAILURE

Much of the disagreement regarding the pathogenesis of symptoms in congestive heart failure revolves about the cardiac output. A reduction in the cardiac output is a primary postulate of the forward-failure theory but reported measurements in patients with congestive heart failure are not in uniform agreement. This is due in part to technical difficulties and the variety of methods used, many of which are undoubtedly inaccurate. (For output measurement, see Chapter 8.)

Ever since the early observations of Lundsgaard,[24] who found a pronounced reduction of the cardiac output in 5 of 6 cases of decompensated valvular heart disease, most reliable investigators have noted a small diminution of cardiac output in the majority of cases of congestive heart failure. Starr and Gamble,[53] using the ethyl iodide method, usually found a depressed cardiac output in patients with heart failure, but in some the values fell within the range of normal. Hamilton et al.[16] calculated the cardiac output from the concentration curve of intravenously injected vital red and likewise found that the output was usually reduced in patients with congestive heart failure. But in some cases with severe symptoms of failure, the output was greater than in other cardiac cases which were well compensated.

Harrison et al.[18] employed a modification of the Grollman acetylene method and observed that the cardiac output of 19 patients with congestive heart failure was usually less than that of 18 normal persons. But they also found normal cardiac outputs in some of the patients with heart failure. There was considerable overlapping of the values of cardiac output in cases of congestive heart failure with those in cases of compensated cardiac disease as well as in normal persons.

A number of recent studies have disclosed a pronounced reduction in cardiac output in advanced heart failure. Thus McMichael,[27] Stewart et al.[56] and Suarez and associates,[58] all using the acetylene method, found a significant diminution in the output of the heart in groups of cases of severe heart failure. However, even these reports reveal some disagreement and overlapping values because Stewart et al.[56] observed cardiac outputs below normal in patients with heart disease without failure and in those recovering from heart failure, while Suarez et al.[58] and McMichael[27] found no significant reduction in compensated cardiac patients and in those with mild heart failure.

Recently Seymour et al.,[48] using a physical method based on the study of pulse tracings and blood pressure,[2] observed a consistent reduction in cardiac

output. Likewise determinations by the direct Fick method (p. 132), using intracardiac catheterization to obtain mixed venous blood, have disclosed more distinct reductions in cardiac output than those determined by the use of acetylene.[28, 21, 32, 55] However, even among these observations there are normal cardiac outputs in some patients with mild grades of heart failure.

These conflicting and indecisive observations have provided material for criticism of the forward-failure theory. For although the cardiac output is usually depressed in cases of heart failure, normal values may be observed in some patients with mild or early heart failure, and some individuals without symptoms or signs of heart failure have cardiac outputs as low as those of certain patients with heart failure. In refutation of these criticisms advocates of the forward-failure theory point out that heart failure is not related to any absolute quantity of cardiac output but to the adequacy of the output for the body requirements. In cases of early or mild heart failure, the cardiac outputs are determined with the patient at rest and may be normal. In such cases symptoms of failure occur only during activity and the cardiac output would probably be found relatively inadequate if it could be determined during the exertion.

Cardiac Failure with High Cardiac Output. Opponents of the forward-failure theory have called attention to groups of cases in which there is an actual increase in cardiac output despite the presence of advanced congestive heart failure. Severe anemia, hyperthyroidism, arteriovenous fistula, beriberi, advanced pulmonary emphysema with arterial anoxemia and pregnancy are conditions frequently associated with an augmented cardiac output. When heart failure develops in such cases, the cardiac output may be less than that prior to failure, but it is still distinctly above normal.[10, 49] In a case of beriberi heart failure presented by Burwell and Dexter,[7] the cardiac output by the direct Fick method was 11.8 liters as compared with a normal of 5.3 liters after clinical improvement.

These observations raise doubt as to the relation of heart failure to a reduction in cardiac output. For it is paradoxical to speak of failure of a heart which is still capable of twice the normal cardiac output. In refutation, advocates of the forward-failure theory point out that an abnormally high cardiac output is necessary in anemia, hyperthyroidism, etc., in order to supply the excessive demands of the body in these conditions. When failure develops, the cardiac output is actually less than previously but still higher than normal. But this output, although elevated, is insufficient for body needs and therefore leads to symptoms of heart failure.[9]

Relation between Changes in Cardiac Output and Severity of Symptoms. If the development of symptoms of heart failure is related to a deficiency in cardiac output, the extent and severity of symptoms should be correlated with the degree of reduction in cardiac output. Furthermore, clinical improvement and deterioration should correspond with an augmentation or diminution in cardiac output, respectively. But Starr and Gamble[53] failed to find a significant relationship between the cardiac output and functional capacity. In the studies of Harrison and associates[18] mentioned above, 15 of the patients with congestive heart failure were restudied after the symptoms of failure had disappeared. With clinical improvement the cardiac output per minute increased in 3 cases and diminished in 7 cases and the output per beat increased

in 9 and diminished in 3; there was no change in the remaining cases. Similarly, McMichael[27] and McGuire, Hauenstein and Shore,[26] using the acetylene method, found no consistent relationship between the degree of reduction of cardiac output and the severity of the symptoms of failure.

Studies of the cardiac output during congestive heart failure led Stewart and co-workers[56] to conclude that the cardiac output closely mirrored changes in severity of symptoms. They determined the cardiac output in 40 patients with valvular heart disease "before, during and after recovery from heart failure" but in only 7 cases were comparative observations made on the same patients during and after recovery from heart failure. A review of these 7 cases fails to disclose an impressive relationship between changes in cardiac output and the severity of symptoms of heart failure.

A more consistent reduction in cardiac output during heart failure and elevation with clinical improvement has been observed by Seymour et al.[48] The mean cardiac output during heart failure was 31 per cent less than after improvement; the output per minute and per stroke increased in every case when heart failure was controlled. McMichael and Sharpey-Schafer[28] and Howarth, McMichael and Sharpey-Schafer,[21] using the method of intracardiac catheterization, observed striking increases in cardiac output in patients with low-output heart failure when the patients were treated by venesection, digitalis or the application of tourniquets. However, these were transient, brief observations over a period of minutes or hours.

Reduced Cardiac Output without Symptoms of Congestive Heart Failure. Additional evidence that the symptoms of congestive heart failure are not directly due to a reduced cardiac output (forward-failure) is the lack of classic symptoms in conditions definitely associated with a great reduction in cardiac output. In various states of shock or collapse due to hemorrhage, trauma or other causes the cardiac output is much lower than in cases of congestive heart failure, yet dyspnea, orthopnea, cardiac asthma, subcutaneous edema and other cardinal features of congestive failure are absent or insignificant. And conversely the symptoms caused by a reduced cardiac output, i. e., by an inadequacy of arterial blood supply to the tissues, such as weakness, mental torpor, fatigability, hypothermia, hypotension, are not observed or are overshadowed in cases of congestive heart failure.

According to the forward-failure theory in its most recent form, symptoms such as weakness and fatigability, directly due to an inadequate cardiac blood supply to the muscles, are present in congestive heart failure but are masked by the symptoms of sodium-water retention. When the latter are eliminated by diuretics, fatigue and weakness become apparent. The absence of dyspnea and edema in shock states despite the low cardiac output may be due to the acuity of the process. Sodium and fluid retention, accountable for dyspnea and edema in congestive heart failure, results only as a secondary effect of *prolonged* inadequacy of cardiac output.

Summary of Criticisms of Forward-Failure and Backward-Failure Theories. In some respects the disagreements between the so-called forward-failure and backward-failure hypotheses are due to differences in emphasis, and preoccupation with different aspects and stages of congestive heart failure. But there are also fundamental differences, particularly as regards the relationship and relative importance of venous pressure and sodium-water retention. Cer-

tain features, such as the relatively normal cardiac output in early cases of heart failure and the localization and sequence of symptoms, are not satisfactorily explained by either theory.

The term "backward-failure" is a confusing one in that it implies a *direction* of flow when actually it refers to a sequence of *locations* of venous congestion. There can be no "backward-failure" without "forward-failure" in a continuous circulation. Hence this contrast of terms should be abandoned. Even if the symptoms of heart failure appear to be due to venous congestion and rising pressure behind a failing chamber, the backward-failure theory omits a series of events, after the initiation of heart failure, without which such congestion could neither occur not persist.

The forward-failure theory, in its present form, does not satisfactorily account for inconsistencies between cardiac output and the occurrence and severity of symptoms of congestive heart failure. The forward-failure theory does not clearly account for the occurrence of isolated left-sided heart failure or for the sequence of development of symptoms. To explain isolated pulmonary congestion (left-sided heart failure) it really invokes the explanation of backward-failure. Merrill[32] stated that the forward-failure theory of salt and water retention "in no way invalidates the 'backward-failure theory' of pulmonary congestion." The major symptoms of heart failure are attributed to sodium-water retention due to forward failure while their localization (e. g., in the lungs) is attributed to a local elevation in venous pressure due to backward failure.

A MODIFIED THEORY OF CONGESTIVE HEART FAILURE

On the basis of present knowledge it is possible to evolve a theory of congestive heart failure which accords with the evidence adduced to support both the forward-failure and backward-failure advocates and which obviates their criticisms.

In such a modified theory, I concur with the advocates of the forward-failure hypothesis that:

(1) Heart failure begins with an inability of the heart to maintain an adequate output; but I believe that up to a certain degree of failure, compensatory mechanisms may restore a normal output.

(2) The reduction in cardiac output is the initiating mechanism responsible for the subsequent manifestations of heart failure.

(3) The retention of sodium and water due to impaired renal excretion is an essential factor in the development of the congestive phenomena of heart failure.

At the same time I believe it is necessary and possible to satisfy the backward-failure adherents by explaining:

(1) The finding of normal cardiac outputs in some patients with heart failure;

(2) The discrepancy between cardiac output and the development and intensity of symptoms of congestive heart failure;

(3) The manner in which isolated left-sided heart failure, presumably associated with a diminished left ventricular output (forward-failure), can lead to venous congestion in and symptoms referable to an organ (the lungs) *behind* the failing chamber;

(4) The relation between elevated venous pressure and sodium-water retention.

Emphasis on two essential points, in addition to those generally accepted, would seem to satisfy the above criteria and reconcile the differences between the forward-failure and backward-failure theories.

1. Various homeostatic mechanisms restore the cardiac output when this tends to become inadequate because of physiologic or pathologic disturbances. In congestive heart failure, an augmented circulating blood volume serves to restore the cardiac output when the fall in output is moderate and sufficient time elapses to permit the development of this compensatory mechanism. *The symptoms of congestive heart failure are due in large measure to difficulties imposed by the compensatory mechanisms and not directly to a deficient output;* hence there is no close correlation between the cardiac output and severity of symptoms except in advanced cases.

2. *The development of increased venocapillary pressure and venous engorgement behind (proximal to) any chamber of the heart is the result of inability of the chamber to accept and eject the venous return of blood as rapidly as it arrives.* Thus the occurrence of pulmonary congestion (and its symptoms and signs) in isolated left-sided heart failure is not the consequence of "backward" failure or back pressure, but of the inability of the failing left side of the heart to propel in a forward direction the increased venous return imposed by an augmented blood volume.

The application of these concepts to the development of the phenomena of congestive heart failure will now be considered in more detail.

Homeostatic Mechanisms Controlling the Cardiac Output

The fundamental function of the heart is to maintain an adequate output of blood for the tissues under all physiologic circumstances. When the heart fails, a variety of compensations are evoked which tend to restore this vital function. Consequently the cardiac output is maintained long after serious circulatory threats and disturbances arise, just as the *p*H of the blood remains constant despite disorders threatening its acid-base balance and just as the blood urea remains normal even when there is moderately severe renal impairment.

The following compensatory mechanisms may restore a deficient cardiac output or may otherwise serve to maintain an adequate blood supply to vital organs.

1. Tachycardia and Cardiac Enlargement. These accommodative mechanisms which increase the cardiac output have been previously discussed (Chapter 2). Like all compensations, cardiac enlargement is valuable in that it preserves a vital function, in this instance a normal cardiac output. It is disadvantageous because it signifies the expenditure of a circulatory reserve and because it is associated with inefficiency in the need and utilization of oxygen.

2. Arteriolar Vasoconstriction. Arteriolar vasoconstriction occurs when there is a reduction in cardiac output. Its compensatory effect is not to restore the cardiac output to normal but to redistribute the diminished output in such a manner as to maintain an adequate blood flow to vital areas. Thus blood is diverted from the periphery and abdominal viscera to the brain and heart.

Arteriolar vasoconstriction is an important compensatory mechanism in conditions which cause such a rapid and intense fall in cardiac output that actual restoration to normal is impossible. The associated clinical picture is acute circulatory failure or shock (Chapter 10). But in chronic congestive failure,

in which the diminution in cardiac output is relatively moderate and occurs gradually, arterial vasoconstriction and redistribution of blood are of minor importance, for other mechanisms can be employed which are capable of restoring the cardiac output to adequate levels.

Arteriolar vasoconstriction may not only serve to redistribute better the diminished cardiac output but also to initiate slower mechanisms which tend to restore an adequate output. In particular, the kidney undergoes arteriolar constriction whenever the cardiac output is diminished. The resulting diminution in renal blood flow has been held responsible for the retention of sodium and water which helps to restore the cardiac output by increasing the blood volume and venous return (infra). Thus a diminution in renal blood flow and retention of sodium and water soon follow not only severe reductions in cardiac output due to hemorrhage or trauma, but also such mild reductions as are associated with assumption of the upright position, prolonged motionless standing, mild exercise and congestive heart failure. In cases of advanced heart failure in which the cardiac output falls significantly despite various compensatory mechanisms, the blood pressure is usually maintained despite the fall in output. This is possible only because of a compensatory increase in total peripheral resistance, i. e., arteriolar constriction. Such increase in resistance is disproportionately great in the renal arterioles.

The mechanism responsible for renal arteriolar constriction is uncertain. It may be induced as part of a generalized splanchnic vasoconstriction which occurs when a diminished output inhibits the vasodepressor mechanism and the carotid sinus vagal arc. Sympathetic stimulation has not been excluded even though renal blood flow in congestive heart failure was not altered by a high spinal anesthesia[34b]; the ephedrine given to maintain blood pressure may have masked or modified any change. It is still probable that there is an important neurogenic (sympathetic) factor in the diminished renal blood flow observed in most cases of congestive heart failure. Humoral agents have also been invoked to account for renal arteriolar constriction in heart failure. Renin has been demonstrated in the renal venous blood of patients with chronic congestive heart failure.[34] Renal arteriolar constriction has also been attributed to the release of vasoexcitor material from the kidney due to renal hypoxia caused by an inadequate cardiac output.[34a]

3. Increased Venous Return. The venous return over a period of time is equal to the cardiac output, for the heart can only pump as much blood as it receives in a unit of time. Factors increasing the venous return tend to increase the cardiac output. The venous return may be augmented by (a) increasing the speed of the circulating blood or (b) increasing the circulating blood volume, i. e., the width of the stream returning at a given speed. When the cardiac output falls or for some other reason is unequal to the demands of the tissues, it may be made sufficient by compensatory mechanisms which increase the venous return either by accelerating the speed of the circulation or by augmenting the volume of the circulating blood.

Increased Speed of Circulating Blood. During exercise or febrile states, the cardiac output is increased largely by acceleration of the speed of the circulation. In certain pathologic states which render the ordinary output inadequate for body requirements, the abnormally high outputs required are attained largely by acceleration of circulating speed, e. g., in cases of hyperthyroidism, anemia, beriberi and arteriovenous fistula. A diminution in peripheral resistance permits the more rapid circulation (p. 102).

Increased Blood Volume. In most conditions leading to chronic congestive heart failure, cardiac enlargement first develops and maintains an adequate output despite cardiovascular disturbances. When this compensatory mechanism is no longer effective or when it is insufficient from the beginning, restoration of cardiac output may follow an increase in the circulating blood volume. In the heart-lung preparation, constriction of the aorta reduces the cardiac output but the output may be restored first by cardiac dilatation and, when this is inadequate, by an increase in the venous return to the heart. In humans also an increase in blood volume by intravenous infusions augments the cardiac output.

Similarly, when the cardiac output falls because of failure of the heart, a progressive enhancement of the circulating blood volume tends to restore the cardiac output. *Thus the blood volume may be represented as a fundamental homeostatic mechanism for maintaining an adequate cardiac output.* The dire consequences of an inadequate cardiac output are avoided but the compensatory mechanism itself, the increased blood volume, leads to symptoms which we know as congestive heart failure. The mechanism by which the circulating blood volume is increased in heart failure and the manner in which it leads to clinical symptoms are discussed in succeeding sections.

Eventually, these homeostatic compensatory mechanisms can no longer maintain an adequate cardiac output. This is due to the fact, noted by Starling,[51] that there is a peak beyond which an increase in venous return does not further enhance the cardiac output (p. 4). Progressive increase in the volume of circulating blood and of the venous return eventually overloads the failing heart. Thereafter, despite an augmented blood volume, the cardiac output diminishes. In part, at least, failure of the increased venous return to be translated into greater cardiac filling and greater output is due to a pronounced rise in pressure within the cardiac chambers. Although the venous pressure may be greatly elevated, the venoatrial pressure difference, which is the effective filling pressure, is diminished in this advanced stage of congestive heart failure.[44]

In the late stages of congestive heart failure, the cardiac output is low despite the body's efforts at compensation. Arterial vasoconstriction and redistribution of the reduced output serve to maintain an adequate blood supply to vital organs. Venous congestion and slowing of the blood stream are notable features. The slowing permits a greater extraction of oxygen from each unit of blood (i. e., the arteriovenous oxygen difference is larger than normal) and this partly counterbalances the diminished blood flow. Actual measurements with the aid of cardiovascular catheterization have shown an increased arteriovenous arterial oxygen not only in the general circulation but also in the renal and hepatic circulations.

Mechanism of Increasing Blood Volume in Congestive Heart Failure

The increased blood volume in congestive heart failure is due both to an increase in erythrocytes and to an enhanced plasma volume.[13, 31] The former may be the result of relatively inadequate blood flow to the bone marrow with a consequent anoxic stimulus to erythrogenesis.

The exact mechanisms which promote an increase in plasma volume are uncertain. The endocrine organs, notably the posterior pituitary but also the anterior pituitary, the adrenal cortex and the gonads, are concerned with water metabolism and water retention and thus probably participate in modifications of plasma volume.[61] The threat of a falling cardiac output to tissue vitality

may be the stimulus to hormone secretions which augment the plasma volume by the retention of water and electrolytes.

However, whether by way of hormonal stimulation or more directly, the kidneys represent the ultimate end organ by which the circulating plasma volume can be enlarged in order to compensate for a falling cardiac output. It is only by retention of fluid, due to a lesser excretion than ingestion of sodium and water, that the plasma volume can be increased and the subsequent congestion and edema of tissues can occur. Heart failure is actually characterized by an impairment of the ability of the kidneys to excrete sodium and water. This has become a cardinal point in understanding both the compensatory mechanisms and the development of clinical features in congestive heart failure. Furthermore our chief advances in the treatment of failure concern the control of sodium-water balance and sodium-water excretion.

Increased Blood Volume and Impaired Renal Excretion of Sodium and Water. The exact mechanism responsible for the impaired renal excretion of sodium and water is of the greatest importance but is still unknown. An understanding of this mechanism could be of great therapeutic value and its investigation should prove fruitful. Three different factors have been considered as the possible mechanism in the renal disability: (1) elevation of renal venous pressure due to congestive heart failure; (2) diminution in glomerular filtration of sodium and water due to reduced renal arterial blood flow; (3) increased tubular reabsorption of sodium and water due to chemical or hormonal influences.

1. Elevated Renal Venous Pressure. Sodium-water retention by the kidney has been attributed to an elevated renal venous pressure and passive congestion of the kidney. An elevated venous pressure has been found by catheterization of the renal vein of patients with heart failure[25a]; these patients also had an elevated right atrial pressure, denoting right-sided heart failure. Partial occlusion of one renal vein in dogs caused a diminution in sodium and water excretion only from the kidney subjected to an increased renal venous pressure (above 150 mm. saline).[64] The disturbances in sodium-water excretion appeared without distinct relation to changes in renal blood flow or glomerular filtration. These observations indicate that heightened renal venous pressure occurs in heart failure and may impair the renal excretion of sodium and water. However, they provide no evidence that an elevated renal venous pressure is the initial cause for the renal impairment or that it is responsible for the early manifestations of heart failure, e. g., dyspnea in pure left-sided failure. Sodium and water retention with consequent dyspnea due to pulmonary congestion occurs in left-sided heart failure when there is no elevation in renal venous pressure. The latter may intensify the renal disturbance later in the course of heart failure when the right ventricle becomes insufficient and the systemic venous pressure rises.

2. Diminished Glomerular Filtration. The studies of Merrill[32] and of Mokotoff, Ross and Leiter,[35] mentioned above, disclosed a reduction in renal blood flow and in the excretion of sodium and water in patients with congestive heart failure. Their calculations led them to conclude that the retention of sodium was due to diminished glomerular filtration consequent to the diminished renal blood flow, and not to increased tubular reabsorption. Tubular reabsorption was found to represent a constant percentage of the glomerular filtrate.

But it should be recalled that great variations in the glomerular filtration of sodium and water are easily neutralized by small deviations in tubular reabsorption. Normally about 99.5 per cent of the sodium and water in the glomerular filtrate is reabsorbed by the tubules. A reduction of 50 per cent in glomerular filtration could be neutralized and a normal sodium excretion effected if the tubular reabsorption diminished merely from 99.5 to 99.0 per cent. To attribute the impaired sodium excretion to reduced glomerular filtration alone it is necessary to prove that tubular reabsorption is absolutely unchanged. But in one of the patients studied by Merrill[32] 99.99 per cent of the sodium filtered by the glomeruli was reabsorbed and in another, 99.96 per cent instead of the normal 99.5 per cent. Similarly the figures of Mokotoff et al.[35] strongly suggest that tubular reabsorption is increased, despite their conclusions to the contrary. I have observed instances in which no sodium was excreted during whole days in patients with congestive heart failure.[11] Significant variations in tubular reabsorption, sufficient to cause considerable retention of sodium, are of such small magnitude that they could easily be obscured by the range of error of the methods now available.

Other objections have been raised to the belief that renal impairment of sodium and water excretion is due entirely or primarily to diminished glomerular filtration. Edema does not occur in many cases of intrinsic renal disease in which glomerular filtration is substantially reduced. This has suggested that a glomerulo-tubular imbalance rather than defective glomerular filtration alone causes sodium-water retention and edema. In occasional cases of congestive heart failure an impairment of renal excretion of sodium and water is observed although glomerular filtration is normal.[49a] Patients in heart failure have been observed to regain clinical compensation without a significant augmentation of their filtration rate,[48, 5a] although the ability to excrete sodium was restored.

It seems probable that diminished glomerular filtration, like elevated renal venous pressure, may contribute to or intensify sodium-water retention but that it is a relatively late factor which appears after heart failure is advanced. When renal blood flow is first diminished, there is a compensatory increase in the proportion of plasma filtered through the glomerulus (i. e., an increased filtration fraction). In consequence, the filtration remains normal at a time when sodium and water excretion are already impaired. There is need for more studies of renal dynamics early in the course of heart failure before there is widespread systemic elevation of venous pressure and systemic congestion.

3. Increased Tubular Reabsorption. Tracer studies with radioisotopes of sodium led Burch, Reaser and Cronvich[6] to conclude that diminished sodium excretion was due to an increased percentage of reabsorption of this electrolyte from the glomerular filtrate. The instances in which I have observed no excretion of sodium at all for twenty-four-hour periods also support this conclusion. The ability of many patients to maintain sodium balance despite impaired glomerular filtration indicates that the percentage of tubular reabsorption of sodium can be regulated independently of filtration.[14a] On the other hand it has been postulated that there is a threshold or limited transfer mechanism for sodium reabsorption in the distal tubule. Thus with increased sodium filtration the distal tubular reabsorptive capacity may be exceeded and more sodium is excreted; with diminished glomerular filtration the small load reaching the distal tubule may be virtually entirely reabsorbed. According to this

view, which is hypothetical, increased tubular reabsorption is determined by impaired glomerular filtration.

Other considerations tend to implicate the tubules rather than the glomeruli as the site of altered sodium-water excretion. Recent evidence indicates that the conservation of sodium is an important tubular function designed to maintain the vital acid-base balance of the body fluids.[50, 39, 40] The excessive formation of acidic substances tends to stimulate the sodium reabsorption function of the tubules. As the cardiac output tends to fall with the onset of heart failure, the initial tissue anoxia and consequent increase in acidic metabolites may act as such a stimulus. Briggs and associates[37a] found evidence that a reduction in oxygen tension of mixed venous blood led somehow to a more complete reabsorption of sodium and water and to consequent cardiac edema.

There is considerable evidence that other threats to bodily homeostasis evoke protective reactions by way of the adrenal cortex and other hormones which are known to act on the renal tubules. Desoxycorticosterone, which probably acts on the tubules, is capable of inducing heart failure when given in excess to patients with Addison's disease (p. 947). A bioassay of adrenal corticoids in the urine of patients with congestive heart failure revealed an increased concentration as compared with normal urines.[37a] A low sweat sodium has been reported in 6 of 7 patients with severe heart failure[32a] and this finding corresponds with that in cases with hyperactivity of the sodium-retaining factor in the adrenal cortex. The adrenocorticotropic hormone of the anterior pituitary (ACTH) has likewise been implicated in the cycle of events causing sodium retention in heart failure. The antidiuretic action of the posterior pituitary on the renal tubule has been held partly responsible for water retention in congestive heart failure. An antidiuretic pitressin-like substance has been found in the urine of patients with congestive heart failure but not in normal controls.[2a] The finding of a vasodepressor material (VDM = ferritin) in the renal vein in heart failure and observation of its antidiuretic action[1] suggested another possible mechanism of renal retention of water.

Investigation of the enzyme systems in the tubules offers a fruitful field for understanding of the renal mechanisms for retention of sodium and water in heart failure. The possible importance of carbonic anhydrase in preservation of sodium and the acid-base balance[39] has led to the administration of sulfanilamide, which specifically inhibits this enzyme; in patients with refractory congestive heart failure this procedure was followed by increased sodium excretion and significant clinical improvement.[47a] The study of glutaminase also seems promising both because of its importance in the metabolism of vital glutamic acid and because of evidence that the adrenal cortical steroids control the action of this enzyme and amino acid. The promotion of sodium-water excretion by mercurial diuretics which act on the tubules suggests that their effect is due to inhibition of enzymes by binding of sulfhydryl groups.

The Relation of Increased Blood Volume to Venous Return and Venous Pressure. The retention of sodium and water over a period of time leads to an increase in the circulating plasma volume. The increased plasma volume precedes any increase in the interstitial fluid. The greater blood volume is accommodated by an enlarged capacity of the venous system. This augmentation of the blood volume, denoting a wider stream of blood, is translated into an

increased venous return to the heart, an effect similar to that of an intravenous infusion or transfusion.

A clear distinction should be made between an increased venous return and an increased venous pressure. The venous pressure is the resultant of two forces, the venous return and the capacity of the receiving cardiac chamber to accept and eject that venous return. A rise in venous pressure occurs when a cardiac chamber cannot handle its venous return.[46, 60, 37] Rarely this occurs with a normal cardiac chamber if there is a sudden and enormous increase in the venous return; more commonly the venous pressure rises in the presence of a diseased or strained chamber with a venous return which is only moderately increased, e. g., by a rapid intravenous infusion.[43, 36] Conversely the reduction of an elevated venous pressure may occur either because the venous return is diminished (e. g., by phlebotomy, the application of tourniquets, or by mercurial diuretics) or because the efficiency of the diseased heart is improved, e. g., by digitalis.

The cause of the elevated venous pressure in heart failure and its relation to the enlarged blood volume are disputed. According to the backward-failure theory as delineated by Starling,[51] the following sequence maintains:

Cardiac failure ⟶ elevated venous pressure and venous congestion ⟶ compensatory arteriolar constriction ⟶ anoxia of bone marrow ⟶ increased blood volume.

The hypervolemia, according to this concept, is secondary to the elevation in venous pressure. But it seems incredible that there can be more than a transient rise in venous pressure and venous congestion unless the blood volume is first increased. For, as blood became impounded behind the failing chamber, the cardiac output and venous return would diminish and thus relieve the venous congestion and reduce the elevated venous pressure. Furthermore, failure of the heart must mean an initial reduction in output as well as a damming of blood within and proximal to the failing chamber. Therefore anoxia of bone marrow or other tissues and organs could be as reasonably attributed to reduced cardiac output (forward-failure) as to arteriolar constriction compensatory to elevated venous pressure (backward-failure).

According to the forward-failure theory the following sequence is postulated:

Cardiac failure ⟶ decreased renal blood flow ⟶ decreased renal excretion of sodium and water ⟶ increased extracellular fluid and increased blood volume.

Merrill[32] accepts this latter sequence of forward failure to account for the increased blood volume but invokes backward failure to account for elevated venous pressure behind the failing chamber. Warren and Stead[63] likewise accept the forward-failure sequence leading to hypervolemia but attribute the elevated venous pressure, first, to venous vasoconstriction and, second, to increased blood volume. It is difficult to understand how there can be an increased volume, which is accommodated exclusively in the venous system, if the veins are constricted. Clinical observations also belie the existence of venoconstriction in congestive heart failure. Furthermore this concept fails to explain why, if venoconstriction and hypervolemia are the causes of increased venous pressure, the venous pressure can be normal in the systemic circulation and elevated in the pulmonary system.

According to the mechanisms which I have outlined above, the sodium

and water retention by way of the kidney occurs as a direct consequence of the initial reduction in cardiac output but not necessarily as a direct consequence of diminished blood flow to the kidney. Hypervolemia results from sodium-water retention and precedes elevation of venous pressure. Hypervolemia increases the venous return. *The venous pressure rises at the entrance to those chambers which are incompetent to receive and expel this augmented return.* There is no venoconstriction. Arteriolar vasoconstriction tends to develop but it has no significant effect on the venous pressure in chronic heart failure. Its chief purpose is to redistribute a diminished cardiac output in favor of the more vital organs and perhaps to promote changes in renal function which result in increased blood volume. (See also p. 101 for effects of exercise.)

Relation of Venous Return and Venous Pressure to Cardiac Output

There is no invariable relationship between *venous return and cardiac output* although as a rule an increase in the former enhances the latter. But when a diseased chamber becomes overloaded, further increase in the venous return may be followed by no increase or a reduction in the cardiac output. The relationship of *venous pressure to cardiac output* is much more indirect. If no other factors were operative, an increased venous pressure would tend to elevate the cardiac output. But changes in venous pressure are the result of other factors and these latter, not the venous pressure, control the output. Thus in an overloaded failing heart, reduction in the venous return by phlebotomy may diminish the venous pressure and increase the cardiac output by permitting the heart to function more efficiently. But in the presence of a normal heart, reduction of the venous return by hemorrhage is associated with an unchanged or diminished venous pressure and a reduction in cardiac output.[1a, 4] Similarly the venous pressure may not change during temporary closure and reopening of an arteriovenous fistula although the cardiac output is quite different in the two states because the healthy heart can handle the smaller or the larger venous return equally well.

In summary, the cardiac output increases as the venous return increases, provided that the competence of the heart is normal or only moderately impaired. With advanced myocardial incompetence, increased venous return may be followed by a reduction in cardiac output. On the other hand the venous pressure may diminish, remain constant or increase as the cardiac output increases, depending on the ratio of the venous return to the competence of the heart in handling the venous return.

Pathogenesis of Left-Sided Heart Failure

Bearing in mind that the onset of heart failure and a reduced cardiac output lead to sodium-water retention, increased blood volume and increased venous return, it is now possible to explain the development of the phenomena of isolated left-sided heart failure, without invoking backward failure.

In certain stages of arteriosclerotic (coronary) heart disease, hypertension and rheumatic aortic and mitral valvular disease, the left chambers of the heart fail while the right chambers are still unimpaired. The early reduction in left-sided cardiac output leads, as just mentioned, to an increased blood volume and venous return. The normal right chambers are competent to receive

and eject this increased venous inflow just as they can accept the increased venous return of exercise or a rapid infusion without a noticeable or persistent rise in venous pressure. Temporarily there is an increased right ventricular output corresponding to the increased venous return.

The increased right ventricular output now returns to the left chambers of the heart as an increased pulmonary venous return. But the failing left chambers cannot competently accept and eject this increased venous return. This disparity, as explained above, leads to an increase in pulmonary venous pressure due to the damming up of blood proximal to the diseased chamber. *The pulmonary venous pressure rises, not because of a "backward pressure" but because the increased venous return, moving in a forward direction, cannot be passed along with normal speed by the failing chamber.* The augmented blood volume becomes concentrated in the pulmonary vascular bed and leads to symptoms of left-sided failure.

In the early stages of isolated left-sided heart failure the increased pulmonary venous return tends to restore a normal left atrial and left ventricular output. But when these chambers become overloaded, the output may fall despite pronounced pulmonary congestion and increased pulmonary venous pressure. During the stage of restored normal left ventricular output, the venous return to the right heart and the right ventricular output are normal. But this normal right ventricular output is added to the pulmonary vascular residual not ejected by the incompetent left chambers. There is thus a constant engorgement or "dilatation" of the pulmonary vascular bed which stimulates the failing left heart to normal output. This is analogous to the mechanism underlying the Law of the Heart whereby a failing chamber dilates and contracts more strongly because a normal inflow is added to a residual from a previously inadequate ejection.

Pathogenesis of Right-Sided Heart Failure

Right-sided heart failure occasionally appears as an isolated syndrome due to pulmonary or pulmonary vascular disease or constrictive pericarditis, but most commonly it is a sequel to left-sided heart failure. The following mechanisms are concerned:

(1) Progressive failure of the left side of the heart leads to prolonged sodium-water retention, augmented blood volume, venous return and pulmonary engorgement, as described above. The pulmonary engorgement is associated with a progressive increase in venocapillary pressure which eventually leads to an increased resistance to outflow from the right ventricle. The increased resistance is disclosed by a pronounced increase in pulmonary arterial pressure. A normal right ventricular output is maintained at first by compensatory dilatation and hypertrophy.

(2) At the same time that the right chambers are being strained by rising pulmonary resistance, the venous return is increasing because of continued augmentation of the blood volume. Eventually the strained right chambers, like the left, cannot normally accept and discharge the augmented venous return. The right ventricular diastolic as well as systolic pressure becomes elevated.[3] The enlarged blood volume accumulates in the systemic veins and the peripheral venous pressure rises. These congestive phenomena account for the clinical features of right-sided heart failure.

Relation of Sodium-Water Retention, Increased Blood Volume and Venous Pressure in Congestive Heart Failure

Proponents of the forward-failure and backward-failure theories differ sharply regarding the relative importance of an elevated venous pressure and of sodium-water retention in producing the cardinal features of congestive heart failure, notably edema. Evidence cited above for the forward-failure theory (p. 83) supports the essential importance of sodium-water retention. According to Warren and Stead[63] salt and water, due to impaired renal excretion, are first retained in the tissues, thus increasing the extracellular (interstitial) fluid. Only subsequently is the venous pressure elevated. This conclusion is based on their observation that in patients just recovered from congestive heart failure, the oral administration of large doses of sodium chloride was rapidly followed by a gain in weight (sodium-water retention) which preceded the rise in venous pressure. Thus they conceive of the sodium-water retention as the basic cause of edema, while elevations in venous pressure determine the localization of the edema.

According to the backward-failure hypothesis, the elevated venous pressure is of primary importance in causing edema; the amount of salt-water retention determines its intensity. (For detailed discussion of pathogenesis of edema, see p. 117). Reichsman and Grant,[42] in studies on patients recently recovered from heart failure, withdrew digitalis instead of administering salt as did Warren and Stead.[63] Unlike the latter Reichsman and Grant[42] observed that the venous pressure rose before there was a gain in weight.

According to the sequence of events I have outlined above there is no conflict over the relative importance of sodium-water retention or of elevated venous pressure. Without sodium-water retention by the kidney in heart failure, there is no increase in blood volume and without the latter there is no pulmonary or systemic venous congestion and no elevation in venous pressure. The elevated venous pressure, which is a cardinal feature of the backward-failure theory, can neither occur nor persist except by virtue of the augmentation of blood volume. This concept is supported by the experiments of Starr, Jeffers and Meade,[54] who found no elevation of venous pressure following severe damage to the right ventricle, and by the observations of Starr,[52] who found a persistent elevation of the venous pressure post mortem in humans who had died from congestive heart failure. The former experiments demonstrated that failure of a chamber, per se, does not cause an elevated venous pressure and the latter observations indicated that even when the factor of cardiac contraction is eliminated by death, the elevated venous pressure of chronic heart failure persists because of the augmented blood volume. Thus salt-water retention, increased blood volume and increased venous pressure are sequential integrated events in heart failure, not independent factors of varying importance.

The quoted observations of Warren and Stead[63] do not prove that edema formation precedes elevation of venous pressure in the development of heart failure. Like these observers I have noted weight gain before elevation of venous pressure in some cases, when large doses of sodium chloride were given to patients just recovered from heart failure. But during the period of weight gain there was a simultaneous prolongation of the circulation time, a diminished vital capacity and the reappearance of orthopnea. In other words there was

pulmonary congestion and elevation of the pulmonary venous pressure before an elevation of systemic venous pressure. The primary weight gain can be interpreted as due to increased blood volume and latent edema, confined at first exclusively or chiefly to the pulmonary tissues. Furthermore the sodium chloride feedings were begun immediately after intense diuresis had caused hemoconcentration, as denoted by an elevated hematocrit. Some of the early weight gain may represent a restoration of a normal hematocrit and not interstitial edema.

In cases of chronic constrictive pericarditis and of tricuspid stenosis, manifestations of advanced right-sided heart failure appear in association with diminished cardiac output, diminished sodium-water excretion and augmentation of blood volume. Nevertheless, significant pulmonary congestion and its clinical manifestations (orthopnea, dyspnea) are often absent. Thus salt-water retention and increased blood volume, by themselves, do not necessarily cause dyspnea, a cardinal and early feature of heart failure. The manifestations of heart failure are limited in these cases to the systemic circulation because the right ventricle cannot receive and eject its venous return. However, the diminished right ventricular output is competently received and propelled by the left heart and pulmonary congestion does not develop.

Relation of Exercise to Pathogenesis of Symptoms of Heart Failure

The commonest first symptom of congestive heart failure is breathlessness on exertion. In the earliest stages there may be no symptoms at all unless the patient is engaging in exercise. This fact has been used to account for some of the apparently paradoxical findings in heart failure.

Thus the observation of normal cardiac outputs in some patients with heart failure is attributed by forward-failure advocates to the fact that the determinations are made with the patient at rest, when his cardiac output may in fact be normal. The presumption is that the output becomes inadequate during exercise, at which time symptoms appear.[19] But since dyspnea occurs promptly, it is necessary to explain how the inadequacy of output is so rapidly translated into symptoms. According to the forward-failure theory this deficient output during exercise leads to a diminished renal plasma flow,[33] an increased tubular reabsorption of sodium[49a] and a consequent salt-water retention by the kidney. But it is implausible that this mechanism would produce an immediate augmentation of pulmonary congestion sufficient to induce clinical symptoms.

The adherents of backward-failure explain the occurrence of dyspnea on exertion by the effects of exercise on the venous pressure.[22] The venous pressure is normal when the cardiac patient is at rest but increases as a result of back pressure during exercise. Such repeated transitory elevations of venous pressure are viewed as reducing the effective blood volume, causing compensatory arteriolar constriction and in some way stimulating an eventual increase in blood volume. But this explanation likewise fails to explain the prompt development of dyspnea during exercise. Even though there may be an elevated systemic venous pressure during exercise,[15] it does not explain how this could immediately increase the pulmonary congestion which is the basis of dyspnea (p. 108).

The dyspnea which occurs promptly on exertion in patients with early left-sided heart failure can be explained according to the modified theory I have outlined. The left side of the heart has a limited reserve and a limited ability

to handle an increased venous return. In early left-sided heart failure a moderate pulmonary congestion exists even when the patient is at rest, but the degree of congestion is below the threshold of causing clinical symptoms.

During exercise there is a prompt increase in the venous return. This increase is mediated entirely or almost entirely by an increased speed of circulation and not by any significant augmentation of circulating blood volume. The opening of vascular channels in the exercising muscle produces the equivalent of arteriovenous shunts which permit a speedier venous return to the heart. This mechanism of increasing the venous return, unlike that of augmenting the blood volume, is immediately significant.

According to principles already mentioned, this increased venous return during exercise need have no effect on the systemic venous pressure if the right side of the heart is competent.[46, 37, 59] But in reaching the low-reserve left side of the heart, it meets obstruction because of the inability of the incompetent left heart to receive and expel the enlarged return of blood. Pulmonary congestion occurs or, if already present, is increased and accounts for the prompt dyspnea. Because of the incompetence of the left heart, the initial increase in venous return under the stimulus of exercise may not be translated into an increased cardiac output. Hickam and Cargill[19] found that in persons with left ventricular failure, there is an elevated pulmonary arterial pressure which is further elevated during exercise, but there is little or no increase in cardiac output.

The Pathogenesis of High Output Heart Failure

The pathogenesis of heart failure, discussed above, refers to cases of primary heart disease in which heart failure is usually associated with some reduction in cardiac output. Special features distinguish the development of heart failure in such conditions as hyperthyroidism, anemia, beriberi, arteriovenous fistula, osteitis deformans and severe pulmonary emphysema, in which the cardiac output is elevated.

These conditions are all characterized by an increased tissue need for blood which can be compensated by an augmented cardiac output. In patients with anemia and severe emphysema the increased need is due to the deficient oxygen content of the blood; in those with hyperthyroidism it is due to increased metabolic requirements; in those with arteriovenous fistula the need arises because a short-circuiting of blood deprives a large area of an adequate blood supply; in those with beriberi a deficient content of thiamine is the apparent cause. In cases of osteitis deformans, the mechanism is that of arteriovenous fistula.[10] The required compensatory increase in cardiac output is effected by an increased venous return. The latter occurs only in part through an increased blood plasma volume and chiefly through an increased speed of the circulation.

In cases of heart failure due to cardiac or valvular disease the initial fall in cardiac output leads to peripheral vasoconstriction and increased peripheral resistance which inhibit speeding of the circulation. Restoration of an adequate cardiac output can only be accomplished by augmentation of the blood volume. In the high-output groups of cases, the initiating disturbance begins in the periphery, not the heart, and results in a diminished peripheral resistance which favors speeding of the circulation. The diminished peripheral resistance may be due to the presence of a shunt (arteriovenous fistula) or to vasodilatation

caused by hypermetabolism, anemia, and the like. The quickened speed of circulation increases the venous return and the cardiac output to the required level. In most of these conditions there is also some utilization of the compensatory effect of an increased plasma volume, depending on the extent to which speed alone can satisfy the excessive demand for blood. Thus an increased plasma volume appears to be stimulated when the compensatory increase in speed does not adequately elevate the cardiac output. The need for this additional compensation probably arises because the acceleration of the circulation diminishes the oxygen utilization per unit of blood flow.

Heart failure occurs when the heart, despite its enlarged output, is no longer satisfying the exorbitant demands of the tissues for blood. When this happens, the same mechanisms described in the low output cases lead to sodium and water retention, hypervolemia and increased venous return in an effort to attain the necessary output. Increased splanchnic arteriolar constriction occurs but is usually insufficient to neutralize the diminished total peripheral resistance. Eventually, as above, the failing heart is unable to handle the increased venous return or to respond with an increased cardiac output. At this point the cardiac output falls from its peak, but despite heart failure the output is still considerably in excess of the usual normal. Plasma hypervolemia becomes associated with the increased speed of circulation. In the low output cases hypervolemia is associated with retarded circulatory speed.

Hypervolemia in Heart Failure and Polycythemia

Hypervolemia has been described as an important compensatory mechanism for maintenance of an adequate cardiac output, but one which eventually leads to the manifestations of heart failure. In polycythemia vera there is a striking augmentation of blood volume but no evidence of heart failure. *However, it is not the increased blood volume per se which accounts for the phenomena of heart failure, but the inability of the diseased heart to accept and expel an increased blood volume.* This leads to venocapillary congestion and the consequent symptoms. In cases of polycythemia with a normal heart, the increased blood volume is competently received and expelled and there is no rise in pulmonary or systemic venous pressure. In addition, the fact that the hypervolemia of heart failure is due largely to increased plasma volume, while that of polycythemia is due entirely to increased cell volume, may be important in determining the presence of heart failure symptoms in the former and not in the latter. It is the transudation of a plasma filtrate, not of whole blood, that leads to edema and other manifestations of heart failure.

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7

THE PATHOGENESIS OF INDIVIDUAL MANIFESTATIONS OF CONGESTIVE HEART FAILURE

PATHOGENESIS OF CARDIAC DYSPNEA

Dyspnea has been defined as subjective distress associated with difficulty in breathing (p. 61). The following discussion concerns not only the mechanisms responsible for the objective abnormalities in pulmonary respiration but also the cause of the accompanying subjective discomfort.

The occurrence of dyspnea in heart failure has been related to three possible mechanisms:

(1) *An inadequate cardiac output and blood flow to the respiratory center stimulates increased respiratory effort;*

(2) *An accumulation of carbon dioxide, a reduction in oxygen or a diminution in the pH of the blood* produces dyspnea by stimulating the respiratory center and/or carotid sinus;

(3) *Pulmonary congestion causes rigidity of the lung* and impairs normal reflex breathing because of mechanical interference with pulmonary expansion and retraction.

Cerebral Blood Flow and Dyspnea

Dyspnea has been attributed to an inadequate cardiac output and consequent ischemia of the respiratory center.[35] But dyspnea is an *early* symptom of left heart failure and in early heart failure the cardiac output is usually normal. The cardiac output falls as heart failure advances. Yet dyspnea may be alleviated when progressive heart failure affects the right as well as the left cardiac chambers. In cases of constrictive pericarditis and, more strikingly, in cases of acute circulatory failure (shock) there is a pronounced diminution in cardiac output with minimal or no dyspnea. Comparative studies of the oxygen content of arterial and internal jugular blood in patients with cardiac dyspnea showed no increase in arteriovenous oxygen difference, as would be anticipated if there were slowing or insufficiency of the cerebral blood flow.[19] Thus the occurrence of dyspnea in heart failure cannot be correlated with a reduction either in cardiac output or in the blood flow to the respiratory center.

Blood Chemical Changes and Dyspnea

Numerous observations indicate that dyspnea cannot be related to chemical changes in the blood which might result from heart failure. The oxygen and carbon dioxide content and the pH of the blood are the pertinent factors. Only the composition of *arterial* blood, which supplies the respiratory center and carotid sinus, is significant.

Arterial Oxygen. Normally the arterial oxygen saturation is 95 to 99 per cent. Although Kroetz[55] found a pronounced reduction in most cases of heart failure, it is more relevant that dyspnea occurred also when the arterial oxygen saturation was normal. Meakins and his co-workers[73] and Fraser and co-workers[36] observed normal oxygen saturations in almost all cases of cardiac dyspnea unless the heart failure was very severe or there were pulmonary complications. Cullen and co-workers[19] discovered no arterial anoxemia even after exercise in patients with slight or moderate heart failure associated with dyspnea.

These observations reveal that the common form of cardiac dyspnea, which appears early in the course of left-sided heart failure, is not due to a reduction in the arterial oxygen saturation or content. Furthermore, low arterial oxygen contents in certain cases of congenital heart disease with cyanosis are frequently unaccompanied by dyspnea. Of course there are instances of heart failure with pulmonary complications, or of congenital heart disease with cyanosis, in which a very low arterial oxygen content is a contributing or major factor in dyspnea. But this is the exceptional not the usual pathogenesis of cardiac dyspnea.

Arterial Carbon Dioxide. Similarly cardiac dyspnea cannot be attributed to an arterial increase in carbon dioxide. The concentration and tension of carbon dioxide in the arterial blood is actually reduced and not elevated. The reduction is a secondary effect of the hyperventilation associated with dyspnea. Only occasionally, with extreme pulmonary congestion and edema or with severe pulmonary emphysema or other extensive pulmonary complications, is there an interference with carbon dioxide elimination and a consequent elevation of its concentration in the blood. In such instances it may contribute to hyperventilation and associated dyspnea.

Hydrogen Ion Concentration. The hydrogen ion concentration of the blood is either normal or slightly diminished (gaseous alkalosis) in cases of cardiac dyspnea due to pure left-sided failure.[37] Therefore arterial acidemia cannot be held accountable for this type of dyspnea. On the other hand, when heart failure is associated with carbon dioxide retention due to extensive pulmonary disease, the hydrogen ion concentration in arterial blood increases (gaseous acidosis). A reduction in the pH of the blood may also result from the accumulation of fixed acids, such as lactic and pyruvic acid, in very advanced or terminal cases of heart failure with pronounced peripheral stasis or in cases of heart failure with renal insufficiency.[35] During exercise, also, patients in heart failure accumulate fixed acids more readily than normally.[29, 74] Under these various circumstances arterial acidemia may produce dyspnea by excessive stimulation of the carotid sinus and respiratory center. However, the dyspnea of acidemia resembles the deep Kussmaul type of hyperventilation seen in diabetic acidosis rather than the usual shallow breathing characteristic of cardiac dyspnea.

Pulmonary Congestion and Rigidity as the Cause of Cardiac Dyspnea

The weight of evidence supports the belief that cardiac dyspnea is due, as a rule, to pulmonary congestion resulting from left-sided heart failure. From the clinical-pathologic viewpoint this concept is supported by the observation that dyspnea is the essential symptom of left-sided heart failure and that pulmonary congestion is the essential pathologic feature.

Pulmonary congestion disturbs respiration either (a) by hampering the diffusion of oxygen and carbon dioxide and thus impairing aeration of the blood or (b) by interfering mechanically with the expansion and retraction of the lungs. We have seen that chemical changes in the blood do not account for the usual cardiac dyspnea and therefore any impairment in aeration is well compensated. It remains to discover by what means mechanical disturbances in pulmonary expansion and retraction account for most instances of cardiac dyspnea.

The Hering-Breuer Reflex. Normal involuntary respiration is dependent on the Hering-Breuer reflex, in which the changing alveolar tension is the stimulus, the vagus nerve is the afferent arc to the respiratory center, and the intercostal and phrenic nerves are the efferent pathways to the intercostal and other muscles of respiration, including the diaphragm. A diminished alveolar tension results in muscular expansion of the chest wall followed by pulmonary expansion due to the increasing negative pleural pressure. The high intra-alveolar tension at the peak of inspiration causes reflex relaxation of the chest wall and the intrinsic elasticity of the lung causes pulmonary retraction.

Pulmonary Congestion and Reflex Stimulation of Respiration. Experimental evidence supports the theory that pulmonary congestion stimulates respiration by way of the Hering-Breuer reflex and thus causes the rapid shallow breathing of cardiac dyspnea. The production of pulmonary congestion in cats[17] and dogs[41] by pulmonary vein ligation and infusion of blood into the pulmonary artery, or by multiple pulmonary embolization,[27, 6] caused rapid shallow breathing which disappeared after section of the vagi. The altered respiration was unassociated with changes in the chemical composition of the blood.

Pulmonary Congestion and the Rapid Shallow Respiration of Cardiac Dyspnea. To understand the manner in which pulmonary congestion induces the rapid, shallow respiration of cardiac dyspnea it should be recalled (1) that the elasticity of the lungs is essential to their easy expansion during inspiration and especially to their retraction during expiration, and (2) that the lung, like erectile tissue, becomes rigid and inelastic when congested with blood.[24, 16] Because of the rigidity of the lungs the normal increase in alveolar tension during inspiration causes relatively less expansion of the alveoli; for the same reason there is relatively less retraction during expiration than normally. Thus the end points of pulmonary inflation and deflation are brought close together, with a consequent shallow respiration.

Were there no compensations, the shallow respiration would be accompanied by inadequate pulmonary aeration and a resulting accumulation of carbon dioxide and deficiency of oxygen in the blood. Since the volume of pulmonary ventilation can be modified only by alteration in respiratory amplitude or in respiratory rate, it is apparent that the reduction in respiratory amplitude in congestive heart failure can be neutralized only by a compensatory increase in rate, i. e., by tachypnea. Thus compensatory tachypnea accounts for our

observation that, despite the shallow respiratory excursions of the inelastic congested lung, homeostasis of the blood with respect to its oxygen content is long maintained in congestive heart failure.

Pathogenesis of Tachypnea in Heart Failure. The exact mechanism by which pulmonary congestion induces tachypnea is uncertain. It seems clear that the first consequence of pulmonary congestion and rigidity is a deficiency in ventilation due to (a) a diminution in the quantity of air inspired and exhaled with each breath, (b) uneven ventilation because less favorably situated alveoli and those which are most rigid are not expanded at all, and (c) impairment of diffusion because of the thickened alveolar septa, encroachment of ectatic wide capillaries on the alveolar spaces and transudation of fluid into the alveoli.

Initially, these disturbances tend to cause a reduction in oxygen and an increase in carbon dioxide content and acidity of the blood. The carotid sinus and respiratory center are chemically stimulated and induce increased respiration. Since pulmonary rigidity prevents or limits augmentation in the depth of respiration, ventilation is enhanced by an increase in the rate. The degree of acceleration is determined largely by the amount of increase in ventilation required to restore the normal oxygen content of the blood. According to this hypothesis chemical changes in the blood do initially stimulate the tachypnea of cardiac failure. But the resulting compensatory ventilation restores chemical homeostasis and accounts for the usual normal findings of arterial oxygen.

It is also probable that vagal reflexes from the congested, rigid lung are concerned in the production of compensatory tachypnea, for in experimental pulmonary congestion rapid breathing no longer is induced if the vagi are cut. Increased sensitivity of the sensory endings concerned with the Hering-Breuer reflex and more frequent stimulation to inspiration and expiration because of the shallow respiratory range may account for the resulting tachypnea. Reflex tachypnea may also be stimulated by increased pressure in the pulmonary veins and left atrium.

If there were a change only in the *quantity* of each breath during shallow respiration of heart failure, then a 30 per cent reduction in amplitude would require a 30 per cent increase in rate to compensate. The total amount of ventilation would be unaltered. However, pulmonary rigidity causes not only a reduction in ventilation, but an inefficiency in ventilation and in diffusion-aeration of the blood. Consequently, in the example mentioned, a 30 per cent reduction in amplitude might require a 50 per cent compensatory increase in respiratory rate. The total quantity of ventilation is increased but the effective aeration of the blood is normal. Since carbon dioxide diffuses more readily than oxygen, the hyperventilation needed to restore the normal oxygen saturation results in an excessive elimination of carbon dioxide.

Relation of Cardiac Dyspnea to Pulmonary Ventilation and Vital Capacity. It has been mentioned that the shallow, rapid respirations of congestive heart failure are associated with an elevated total ventilation. Peabody and his associates[80] also demonstrated that the vital capacity is reduced and that there is a close correlation between the degree of reduction and the severity of dyspnea. Christie and Meakins[16] showed that in patients with congestive heart failure the vital capacity was a gauge of the rigidity of the lungs. The reason for this is apparent since the vital capacity is the maximal quantity of air that can be exhaled in a single expiration after a maximal inspiration. As we have seen, rigidity of the lung diminishes both its degree of expansion and its degree of re-

laxation in response to corresponding motions of the chest wall and diaphragm. The intensity of dyspnea has been correlated not only with the reduction in vital capacity but also with the increase in rate and total ventilation. Harrison and his co-workers[43] observed that dyspnea usually occurred when the ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ exceeded a given value. More recently an excellent correlation has been found between the occurrence of dyspnea and the ratio of breathing reserve to maximal breathing capacity. The latter averages 100 liters per minute for normal females, and 150 liters per minute for normal males, and is determined by having the patient breathe in and out as fast and deeply as possible for 5 to 20 seconds. The breathing reserve is the maximal capacity minus the actual ordinary minute ventilation in any given state. In congestive heart failure there is both a reduction in maximal breathing capacity and an increase in actual ventilation; the breathing reserve is diminished by both of these changes.

This correlation between the severity of dyspnea and quantitative changes in respiration does not denote that the dyspnea is caused by these changes. The increased respiratory rate and diminution in vital capacity and maximal breathing capacity are *consequences* of pulmonary congestion and rigidity just as is the dyspnea. These and other quantitative changes in pulmonary respiration are merely indices of the pulmonary rigidity. It is the pulmonary congestion and rigidity per se which cause dyspnea.

Pathogenesis of Subjective Distress During Dyspnea

The mechanisms discussed above attempt to explain the pathogenesis of the rapid shallow breathing and the objective disturbances in ventilation associated with dyspnea, but do not reveal why the patient suffers distress. An obvious suggestion is that respiratory distress occurs when the pulmonary system is unable readily to meet the demands of the tissues for ventilation. Actually, the evidence mentioned above fails to show that the demands for tissue oxidation are unsatisfied in most cases.

The most probable causes for subjective discomfort are the excessive work of the muscles of respiration and the use of muscles not ordinarily required in unconscious breathing to distend and deflate the rigid lungs. The increased intrathoracic pressure resulting from the loss of pulmonary elasticity[16, 86] and the increase in the number of respirations per unit time add to the burden. The localization of the distress in the upper abdomen, chest wall and neck seems to confirm the impression that the subjective discomfort with dyspnea arises from fatigue of the muscles of the chest wall and of the diaphragm. The exaggerated work of the respiratory muscles accounts for most of the increased oxygen consumption in dyspneic patients.

Production of Dyspnea during Right-Sided Heart Failure

Dyspnea is usually present in patients with right-sided heart failure. As a rule it is due to persistence of the pulmonary congestion of left-sided heart failure, since the latter usually precedes right-sided heart failure. But following failure of the right ventricle, the dyspnea may be partially alleviated in proportion to the relief of pulmonary congestion.

In some cases right-sided heart failure is secondary to primary pulmonary

disease such as extensive emphysema, fibrosis, etc. The dyspnea may then be caused entirely by the pulmonary disease and not by failure of the right side of the heart.

In addition to the contributions of preexisting pulmonary congestion or of intrinsic pulmonary disease to the production of dyspnea in patients with right heart failure, the latter itself may contribute as follows:

(1) Severe peripheral venous stasis may cause a significant reduction in the oxygen tension and an increase in the carbon dioxide tension of the venous blood returning to the lungs. The combination of pulmonary congestion and severe tissue stasis cannot be adequately compensated and the oxygen saturation of the arterial blood is significantly reduced. The resultant anoxemia of the respiratory center may contribute to the occurrence of dyspnea.

(2) Severe venous stasis with right-sided heart failure may lead to an increase of lactic acid in the blood. This may increase the hydrogen ion concentration of the blood, especially in hypertensive patients with renal damage. The change in chemical composition of the blood stimulates the respiratory center and may cause hyperventilation and dyspnea.

(3) Right-sided heart failure is associated with a rise of pressure in the venae cavae and right auricle. Harrison and his associates[42] found that when they elevated the pressure in the venae cavae by the rapid injection of fluid or by insertion and inflation of a balloon, there was an increase in respiration which did not occur if the vagi were sectioned. These experiments suggest that an elevation of pressure in the venae cavae and right auricle, such as occurs with right-sided heart failure, may reflexly stimulate breathing and therefore may contribute to the development of dyspnea.

(4) Hydrothorax, ascites and extreme and sudden hepatic enlargement occurring during right-sided heart failure may precipitate or accentuate dyspnea, by interfering with the distensibility of the lungs.

Relation of Effort to Cardiac Dyspnea

In its early stages cardiac dyspnea is usually initiated only after exertion, which, however, did not cause dyspnea before the patient's heart failed. Pulmonary congestion with consequent rigidity of the lungs is the fundamental basis for cardiac dyspnea whether it appears during rest or after exercise. The patient with left-sided heart failure experiences pulmonary congestion, even at rest, but it may be insufficient to produce dyspnea. During exercise this congestion is further increased until the patient experiences dyspnea. Thus very severe pulmonary congestion may cause dyspnea at rest; with lesser degrees of congestion, dyspnea only occurs when pulmonary congestion is intensified to the symptom level by exercise or other means.

Exercise increases pulmonary congestion by augmenting the venous return. If the right heart is competent this augmented return is effectively expelled into the already congested lung while the weak left heart is unable to drain effectively the pulmonary venous return. For this reason pulmonary congestion and dyspnea are usually most intense when failure is limited to the left heart. Psychic stimulation of respiration, increased production of lactic acid, reflexes from the muscles,[18] and reflexes stimulated by an increase in venous pressure have also been suggested as factors in the dyspnea induced by exercise.[19, 42]

PATHOGENESIS OF ORTHOPNEA

Since essentially the same factors are concerned in the pathogenesis of orthopnea as of any other form of dyspnea, we will consider only the role of the recumbent position in the promotion of dyspnea. Again it must be emphasized that, like dyspnea, cardiac orthopnea is a cardinal symptom of left-sided heart failure and is due fundamentally to pulmonary congestion. Furthermore, when the right side of the heart fails and pulmonary congestion is relieved, orthopnea is often alleviated despite the elevation of venous pressure, peripheral tissue stasis and other related phenomena.

1. Increased Pulmonary Congestion in Recumbent Position. There is considerable evidence that there is a shift of blood from the upper half of the body to the splanchnic area and lower extremities with assumption of the erect position, and the reverse with recumbency.[28] This gravitational shift of blood is noted clinically in the altered degree of filling of the superficial veins of the extremities and was demonstrated plethysmographically by Atzler and Herbst.[3] The circulating blood volume is increased in the recumbent position.[110, 81] It may be presumed that in the recumbent position the shift of blood to the thorax from the lower extremities and splanchnic viscera increases pulmonary congestion. Most significant are the observations that the cardiac output, and therefore the venous return, are augmented when an individual changes from an upright to a recumbent position.[71] In the presence of left-sided failure, such an increase in venous return intensifies pulmonary congestion as explained under the effect of exercise.

Gravity not only affects the distribution of blood between the thorax and lower half of the body but also between the heart and lungs within the thorax. Dock[21] pointed out that when a person is recumbent the blood from the pulmonary venous bed must be *elevated* 4 to 7 cm. against gravity to reach the left ventricle, while when the person is erect the blood *descends* 3 to 5 cm. Because of this gravitational disadvantage of blood flow from the lungs to the left ventricle there is a relative increase in pulmonary congestion in the recumbent position.

Confirmation of increased pulmonary congestion in the recumbent position is offered by comparative measurements of vital capacity when patients with orthopnea are erect and supine. Christie and Beams[15] found that while the vital capacity in normal persons was diminished 5 per cent by a shift to the horizontal position, there was an average fall of 25 per cent in patients with orthopnea. This observation has been confirmed by others, including Calhoun and his co-workers.[13] Since the diminution in vital capacity is a measure of the degree of pulmonary congestion and rigidity of the lung, these changes in vital capacity indicate an increase in pulmonary congestion with assumption of a horizontal position. Adoption of the recumbent position by increasing the pulmonary congestion and rigidity already present in patients with heart failure either initiates or intensifies dyspnea by mechanisms already discussed.

2. Mechanical Interference with Pulmonary Ventilation in Recumbent Position. When the patient with cardiac orthopnea reclines, the diaphragm is elevated and consequently interferes with thoracic breathing by shortening the thoracic compartment available for expansion.[70] The mechanical factor is especially important in the presence of cardiac ascites, enlarged liver and abdominal

tympanites which not only elevate the diaphragm but also interfere with diaphragmatic breathing.

PATHOGENESIS OF PAROXYSMAL DYSPNEA AND CARDIAC ASTHMA

Relation to Pulmonary Congestion. This discussion is concerned with the paroxysmal attacks of dyspnea which, as a rule, occur at night and wake the patient from sleep. As indicated by Hope,[47] who first employed the term "cardiac asthma," pulmonary congestion is the fundamental basis of these attacks as it is for dyspnea at rest or on exertion. That cardiac asthma results from pulmonary congestion is indicated by its occurrence almost exclusively in patients with hypertensive, aortic valvular or coronary artery disease or other conditions which are complicated by left-sided heart failure. Circulatory studies on patients between attacks of cardiac asthma also show that they are suffering from pulmonary congestion. Weiss and Robb[105] found that there was an increase in the volume of blood in the lungs, a retardation of the pulmonary blood flow, and a reduction in vital capacity. On the other hand, the systemic circulation is unchanged since the stroke and minute volume, the velocity of peripheral blood flow, the arteriovenous difference and the systemic venous pressure are all normal in the great majority of cases. Furthermore, the observations of Weiss and Robb, and of Calhoun et al.,[13] have shown that neither a diminished blood flow to the respiratory center nor changes in blood gases can account for cardiac asthma.

Clinical and circulatory observations reveal that *during* the attacks of cardiac asthma the severity of pulmonary congestion is increased. Pulmonary râles appear or become more extensive. The second pulmonic sound becomes more accentuated and may be louder than the second aortic sound, even when hypertension is present. The low vital capacity is further diminished during the attacks. The velocity of blood flow in the lungs is diminished and there is an increase in the volume of the pulmonary vascular bed, indicating an intensification of pulmonary engorgement.[105]

The actual precipitation of an attack of cardiac asthma is due to some factor or factors which intensify the preexisting pulmonary congestion sufficiently to cause clinical dyspnea. Such factors usually intensify pulmonary congestion by enhancing the venous return.[30] In addition variations in the sensitivity of the respiratory center, e. g., during sleep, are also concerned both in the initiation and subsidence of an attack of cardiac asthma.

Mechanism of Precipitating Factors in Paroxysmal Dyspnea or Cardiac Asthma. *Recumbency.* Often the patient suffers from orthopnea while awake and therefore goes to sleep while propped up on pillows. The attack of dyspnea is precipitated when he slides down during sleep to a more horizontal position. The significance of this factor is confirmed by the frequency and rapidity with which an attack is relieved as soon as the patient sits up or gets out of bed to go to a window. The mechanisms involved were discussed under orthopnea. The main factor is a redistribution of blood which increases the return to the right side of the heart and lungs.

Sleep. A characteristic feature of cardiac asthma is its occurrence after patients fall asleep. It has been assumed that the diminished irritability of the central nervous system when the patient is asleep permits the lungs to become much more engorged as a result of recumbency than when he is awake. When the patient is awake, reflex hyperventilation and slight dyspnea appear before

pulmonary congestion is intense and the patient consciously or unconsciously assumes a somewhat oblique if not completely vertical position. During sleep, however, the degree of congestion may become so great as to be associated with bronchial spasm, edema and transudation into the alveolar spaces. Then the resumption of the erect position may not be adequate to stop the attack immediately.

Cough. In my experience cough is usually manifested after the attack has already begun and is not a precipitating factor.

Terrifying dreams during sleep have been said to precipitate an attack, perhaps by causing an elevation in blood pressure. This factor cannot be evaluated. Furthermore nightmares occur frequently in cardiac patients who do not experience nocturnal dyspnea.

Diminished Muscular Activity. Christie[14] has suggested that diminution of muscular activity during sleep causes venous stagnation within the muscles. The attacks may then be precipitated by *sudden muscular movement* with a consequent increase in venous return.

Increased Blood Volume. An increased blood volume due to the resorption of latent edema when the patient becomes recumbent at night may be an important cause of paroxysmal dyspnea according to Brunn[11] and others. This would have the effect of increasing the venous return and thereby the degree of pulmonary congestion. The fact that the attacks may be diminished or prevented by a low sodium intake and vigorous diuresis jibes with the belief that an augmented blood volume is important in the underlying pulmonary congestion.

Cardiac asthma is a term applied to those attacks of nocturnal dyspnea which are characterized by wheezing respirations and audible rhonchi in the chest. The asthmatic type of respiration may be due to intense congestion and swelling of the bronchial wall, to a serous exudation and/or to bronchospasm.[83] It is uncertain whether this asthmatic dyspnea is due to vagal reflexes from the congested lung to the affected bronchi, to congestion and increased hydrostatic pressure in the bronchial capillaries due entirely to left-sided failure, or whether it appears only when intense pulmonary congestion occurs in predisposed allergic persons.[97]

PATHOGENESIS OF ACUTE PULMONARY EDEMA

Attacks of acute pulmonary edema are essentially severe episodes of paroxysmal dyspnea which are due to the same fundamental factor of sudden intensification of the pulmonary congestion of left-sided heart failure. This concept is supported by the frequent occurrence of pulmonary edema in the same patients as suffer from cardiac asthma, its development under similar circumstances (except that it occurs at any time of the day and not necessarily after retiring), and the common transition of an attack of cardiac asthma into one of pulmonary edema.

The precipitation of pulmonary edema by intravenous infusions of saline or plasma or by transfusions of blood, and its occurrence in mitral stenosis after strenuous exertion, during pregnancy or post partum supports the theory that pulmonary edema like cardiac asthma may be elicited by a sudden augmentation of the venous return and intensification of pulmonary congestion. Conversely, acute pulmonary edema is often relieved by venesection or the application of tourniquets to the extremities—factors which reduce the venous

return. Experimentally, Welch[106] long ago demonstrated in rabbits that pulmonary edema could be produced by compression of the left ventricle or aorta and by ligation of most of the pulmonary veins, procedures which diminished the left ventricular output and caused intense pulmonary congestion.

The chief difference between pulmonary edema and cardiac asthma is the occurrence in the former of a much more extensive exudation of edema fluid around the septal vessels, within the alveoli, in the bronchial walls and in their lumens. The edema results from a pronounced increase of the hydrostatic pressure in the pulmonary capillaries, due to the intensification of pulmonary venous engorgement. The relatively high protein content (2 to 4 per cent) in edema fluid suggests that increased permeability of the vessel walls facilitates the formation of pulmonary edema.[23]

Pulmonary edema and cardiac asthma occur much less frequently in left-sided heart failure due to mitral stenosis than in cases of left ventricular failure, despite the presence of longstanding congestion in the former. Several factors may explain the relative rarity of pulmonary edema in mitral stenosis.

The left ventricle does not fail; it expels as much blood as it can receive through the stenotic mitral valve. The left atrium undergoes progressive enlargement, which at first compensates for the stenosis and later offers a huge storage place preventing the sudden accumulation of blood in the lungs. Because of the absence of valves between the left atrium and pulmonary veins, mild pulmonary congestion is a very early occurrence and its increase is a gradual one over many years. This prolonged interim permits the development of anatomic and functional adjustments which are better able to cope with sudden flooding of the pulmonary circulation. The lungs in mitral stenosis gradually develop extensive fibrosis, with thickened alveolar septa which interfere with the transudation of fluid into the alveoli. Finally, the right ventricle fails early in mitral stenosis. Since the most favorable combination for the development of pulmonary edema is failure of the left heart with good function of the right heart, pulmonary edema does not occur readily in mitral stenosis with its early right-sided cardiac strain. Nevertheless these differences are relative and pulmonary edema may occur in mitral stenosis if the augmentation of venous return and congestion is sufficiently rapid and pronounced, e. g., during extreme exertion, and during pregnancy and post partum.[95, 68]

Other Theories of Pulmonary Edema. Pulmonary edema is not invariably due to left-sided heart failure. It may occur (a) in pneumonia and in poisoning with certain war gases (phosgene) and especially (b) in certain diseases of the brain such as trauma, tumors, hemorrhage and encephalitis. In the former group local damage to pulmonary capillaries may predispose to edema by increasing capillary permeability; its occurrence in the latter suggests a neurogenic mechanism which could likewise promote permeability. The pulmonary edema of clinical left ventricular failure has also been attributed to neurogenic reflexes arising in the root of the aorta, the carotid receptors, the pulmonary artery and large veins and in the left ventricle.[104, 66] Wassermann[104] described observations on patients whose attacks of paroxysmal dyspnea were relieved by section of the depressor nerves and by pressure over the carotid sinus.

In my opinion there is convincing evidence favoring sudden intensification of pulmonary congestion as the fundamental cause of the pulmonary edema in clinical cases of left-sided heart failure. The efficacy of a reduction in blood volume and venous return by sodium restriction, mercurial diuresis, venesec-

tion or the application of tourniquets in preventing and controlling pulmonary edema has been mentioned. However, the prompt therapeutic effectiveness of morphine in many cases is noteworthy and suggests some causative role of the nervous system in the production of cardiac asthma and pulmonary edema. But special aortic, carotid, ventricular or other vascular reflexes need not be postulated. The theory of pulmonary congestion as the basis of pulmonary edema has necessarily included the sensitivity of the respiratory center in mediating the efferent neural arc which effects increased respiratory rate and ventilation. Since the compensatory tachypnea must be mediated through the respiratory center, morphine provides relief by depressing the sensitivity of this center to the stimuli which induce increased respiratory ventilation.

The pathogenesis of acute pulmonary edema occurring in conditions other than left heart failure may have a pathogenesis unrelated to pulmonary congestion, e. g., toxic or neurogenic increase in capillary permeability.[23]

PATHOGENESIS OF CHEYNE-STOKES RESPIRATION

Two factors are concerned in the development of Cheyne-Stokes respiration: (1) a diminished sensitivity of the respiratory center and (2) a relatively inadequate concentration of carbon dioxide to stimulate the respiratory center.

Diminished Sensitivity of Respiratory Center. Cheyne-Stokes respiration is not a specific feature of congestive heart failure. It is seen most frequently in patients with cerebral tumors and other cerebral lesions and in elderly patients with cerebral arteriosclerosis who receive morphine or other strong cerebral depressants. Sleep is a predisposing factor because it is associated with a diminished sensitivity of the respiratory center. The relief of Cheyne-Stokes respiration by aminophylline is probably due to improved cerebral blood flow and consequent improvement in the tone of the respiratory center.

Inadequate Respiratory Stimulus (Acapnia). With *severe* depression of the respiratory center, even a normal content of carbon dioxide in the blood may be insufficient to stimulate the center; following temporary apnea periodic breathing may be induced. With lesser degrees of medullary depression, Cheyne-Stokes respiration is precipitated only if there is a reduction in the carbon dioxide tension, i. e., if there is a diminution in the normal respiratory stimulus. In cases of congestive heart failure with dyspnea, overventilation results in an excessive pulmonary elimination of carbon dioxide and consequent reduction in its arterial concentration (acapnia). When diminished responsiveness of the respiratory center (due to sleep, morphine, cerebral arteriosclerosis) is combined with a deficient respiratory stimulus (due to hyperventilation in left-sided heart failure), a period of apnea is produced and periodic breathing follows.

The Cycle of Cheyne-Stokes Respiration. The subsequent waxing and waning of periodic respiration is explained as follows: During the initial apnea, there is a progressive reduction in arterial oxygen saturation. Arterial anoxemia stimulates the carotid sinus and thereby the respiratory center to resume respiration. At the same time an increase in carbon dioxide tension during the apneic phase directly stimulates the respiratory center. This sudden and exaggerated stimulation of the respiratory center by both anoxemia and excess of carbon dioxide results in an overshooting of the crescendo phase of respiration, with resulting hyperpnea. This exaggerated hyperpnea again excessively

reduces the carbon dioxide content of the blood and is followed by waning respiration, apnea and a repetition of the cycle.

The importance of the carbon dioxide content of the blood in the pathogenesis of Cheyne-Stokes respiration is indicated by the following observations: Cheyne-Stokes respiration can be induced by voluntary overventilation which reduces the blood carbon dioxide tension;[22] overventilation in an atmosphere containing 5 per cent carbon dioxide fails to cause this type of periodic breathing; the administration of carbon dioxide abolishes Cheyne-Stokes respiration;[2] the carbon dioxide tension of arterial blood is reduced in patients with Cheyne-Stokes respiration.[44]

Anoxemia. Arterial anoxemia does not initiate the attack, for the oxygen saturation is normal in patients with heart failure who are subject to Cheyne-Stokes respiration, and the administration of oxygen does not abolish the attack. But arterial anoxemia is important in causing the crescendo phase, after apnea has been initiated by a reduction in carbon dioxide in a patient with a hyposensitive respiratory center. Oxygen given during Cheyne-Stokes breathing only modifies it by prolonging the apnea and making the hyperpnea less stormy.[102] For the anoxic stimulus to overventilation is removed and the latter is produced only by the excessive carbon dioxide which accumulates during apnea.

Cheyne-Stokes Respiration and the Adams-Stokes Syndrome. Cheyne-Stokes breathing sometimes occurs in connection with the Adams-Stokes syndrome in complete heart block. During the prolonged period of cardiac arrest, celebral ischemia depresses respiratory irritability. At the same time the arterial anoxemia, which develops during circulatory standstill, results in hyperventilation and excessive elimination of carbon dioxide. When the heart resumes beating, the respiratory center is relatively insensitive and the blood which is propelled to it is deficient in carbon dioxide. These are the factors initiating the apnea of Cheyne-Stokes respiration.[46, 34] Hyperpnea and dyspnea occur during cardiac standstill and apnea during resumption of cardiac contraction.

PATHOGENESIS OF CARDIAC EDEMA

Sodium-Water Retention. Cardiac edema has long been attributed primarily to an increased venous pressure and consequently to an elevated hydrostatic pressure within the capillaries.[99, 65] In recent years emphasis has shifted to the importance of sodium and water retention within the body, for without it generalized edema cannot occur. The discovery that in congestive heart failure there is an impaired renal excretion of sodium[39, 76, 89] has called attention to the importance of the kidney in the edema of heart failure (p. 83) and has led to a revision of previous sharp distinctions between renal and cardiac edema. The therapeutic efficacy of extreme reductions in sodium intake and likewise of mercurial diuretics, which produce a notable increase in sodium excretion, has reinforced the belief that sodium balance is the cardinal factor in the production and disappearance of edema. Similarly the production of edema in patients with Addison's disease by excessive dosage of desoxycorticosterone and sodium (p. 947) stresses the importance both of sodium and renal function, because desoxycorticosterone promotes renal tubular reabsorption of sodium.

The possible manner in which cardiac failure impairs the renal excretion of sodium and water and leads to edema has been discussed in detail in the

chapter on pathogenesis of heart failure (p. 94). In the same chapter the relative importance of sodium-water retention and of elevated venous pressure in the pathogenesis of cardiac edema was considered. In brief, it was concluded that sodium-water retention is a primary prerequisite for the development of edema, but edema is not necessarily a *direct* consequence of salt-water retention. Hypervolemia, increased venous return to an incompetent cardiac chamber and increased venous pressure are a sequence of events which determine the appearance and localization of edema after renal retention of sodium and water occur.

Increased Venous Pressure. The studies of Starling[99] showed that a passage of fluid from the capillaries into the tissues occurred when the hydrostatic pressure within the capillaries exceeded the colloid osmotic pressure of the serum protein. Thus the accumulation of fluid in the tissues may be due either to an elevation of capillary hydrostatic pressure or to a diminution of serum proteins or both. Normally there is a gradual fall of pressure as the blood passes from the arterial limb to the venous limb of the capillaries and thence to the great veins. According to the direct microscopic studies of Landis,[59] the pressure in the arterial limb of the human capillary is about 42 cm. of water and in the venous limb about 16 cm. of water. Since the colloid osmotic pressure is about 30 cm. of water,[53] the equilibrium between the two factors is normally such as to cause fluid transudation into the tissues at the arterial limb and fluid resorption at the venous limb.

The normal pressure in a medium-sized subcutaneous vein is about 4 to 8 cm. of water. In cases of heart failure associated with subcutaneous edema the venous pressure commonly rises to between 15 and 25 cm. of water and sometimes higher. According to the studies of Fahr and Ershler,[32] who used Landis' method for measuring capillary pressure, edema tends to develop when the hydrostatic pressure in the venous end of the capillary is 26 cm. of water, which corresponds to a pressure in the arm vein of 17 cm. of water. There is a corresponding rise in the hydrostatic pressure of the capillaries so that it greatly exceeds the colloid osmotic pressure of the blood in the venous as well as the arterial limb. The result is a transudation of fluid into the tissue spaces with consequent edema.

The belief that edema forms because of increased venous (and therefore capillary) hydrostatic pressure is based on considerable experimental and clinical evidence.[94] Venous ligation in animals and humans, which causes a local rise in venous pressure, has resulted in edema of the affected subcutaneous tissues.[75, 26] Landis[59] showed that when the hydrostatic pressure in the capillaries of the frog's mesentery exceeded the colloid osmotic pressure of the blood, there was a transudation of fluid out of the capillaries. Quantitative plethysmographic studies on humans by Krogh, Landis and Turner[56] revealed that after compression of an extremity fluid accumulated in the tissue spaces when the venous pressure exceeded 15 to 20 cm. of water, a pressure similar to that seen frequently in patients with right-sided heart failure.

The importance of an elevated venous pressure in causing cardiac edema is demonstrated clinically by the frequency of edema in patients with right-sided heart failure, in whom the elevated venous pressure is a characteristic feature, and by the absence of subcutaneous edema in patients with left-sided heart failure whose systemic venous pressure is normal. On the other hand pulmonary edema occurs frequently in cases of isolated left-sided heart failure

in which an elevation of the venocapillary pressure is limited to the pulmonary circulation. That a diminished blood supply to the tissues is not a causative factor appears clear from the absence of edema in patients with shock due to acute circulatory failure. The greater frequency and intensity of cardiac edema in the lower extremities of ambulant patients may also be explained by the higher venous and capillary pressure due to gravity.

The essential causal relationship of an elevated venous pressure to cardiac edema has been questioned, particularly by those who oppose the backward-failure hypothesis. Altschule[1] emphasized that while in general there is a correlation between increased venous pressure and the presence of edema there is considerable overlapping of the values of venous pressure in edematous and nonedematous patients. In many edematous patients the venous pressure was no higher than in patients without edema. Only when the venous pressure rises as high as 30 to 40 cm. of water does Altschule believe it may be considered solely responsible for the formation of cardiac edema. One possible explanation for these discrepancies is the variation in venous pressure according to the patient's activity.[60] Isolated measurements of venous pressure made with the patient at rest do not reflect these variations. Shifts in edema fluid occur much more slowly than changes in venous pressure dependent on rest and exercise. Variations in sodium intake, tissue pressure and other secondary factors may also account for incomplete correlations between degree of elevation of venous pressure and of edema.

Another objection to the importance of elevated venous pressure in causing edema was raised by Ray and Burch,[88] who found that following ligation of the inferior vena cava to prevent pulmonary embolism, edema usually disappeared even when there was a persistent and intense elevation of the venous pressure in the lower extremities. However, it is more significant that edema did occur soon after the venous ligation, concomitant with the elevation in venous pressure. Subsequent disappearance of edema may have been due to efficient lymphatic drainage. The situation is not analogous to that in congestive heart failure in which the elevated venous pressure is not local but universal throughout the systemic circulation.

Reduction in Colloid Osmotic Pressure. Normally the force of hydrostatic pressure which tends to cause an escape of fluid from the capillaries is counterbalanced by the colloid osmotic pressure of the blood proteins, which tends to draw fluids from the intercellular tissue into the capillaries. The colloid osmotic pressure develops because the blood is separated from the intercellular tissue fluids by a membrane (the capillary wall), which is relatively impermeable to protein. The plasma albumin is most important in producing osmotic pressure, because its concentration is greater than that of the globulin and because its molecule is smaller. The normal colloid osmotic pressure is between 30 and 34 cm. of water, which is about equal to the average hydrostatic capillary pressure, less than the capillary pressure at the arterial end and more than the venocapillary pressure.

A sharp reduction in blood proteins, especially in plasma albumin, and the resulting diminution in osmotic pressure may permit the unbalanced hydrostatic capillary pressure to cause an escape of fluid into the tissues. Subcutaneous edema has been produced experimentally in animals by plasmapheresis.[63, 4] The edema associated with certain nephrotic states and with starvation has been attributed to the very low blood proteins in these conditions. But there

is often a lack of correlation between the severity of the edema and the diminution in proteins; the edema may disappear while the proteins are still low.

In cases of congestive heart failure there is often a reduction in the concentration of plasma protein, especially of the important albumin fraction.[91, 93, 45] In general the reduction in blood proteins in most cases of heart failure is relatively small but occasionally it is pronounced, as in cases of constrictive pericarditis. A corresponding diminution in the colloid osmotic pressure was demonstrated by the direct measurements of Iversen and Nakazawa.[48]

According to Payne and Peters,[79] the reduction in plasma proteins is caused chiefly by malnutrition due to anorexia, low protein intake and vomiting. Pronounced passive congestion of the intestinal mucosa may somewhat impair the absorption of amino acids. Prolonged loss of small amounts of albumin in the urine and in pleural and peritoneal exudates may also decrease serum albumin. Finally, longstanding congestion and anoxemia of the liver may impair its ability to elaborate serum protein. A reduction in serum proteins does not, in itself, cause edema unless the concentration falls below 5 gm. per 100 cc. (albumin below 2.5 gm. per 100 cc.). Therefore the lesser degrees of hypoproteinemia often seen in patients with congestive heart failure are usually insufficient to produce edema and at most represent a minor accessory causative factor. But when hypoproteinemia is pronounced, correction of this factor may be important in controlling edema.

The colloid osmotic pressure of serum proteins is somewhat neutralized by the osmotic pressure of the protein in tissue fluid. However, the protein content of the latter is much less (about 0.5 per cent) than that of serum protein and its osmotic pressure is only about 3 cm. of water as compared to 30 cm. for the colloid osmotic pressure of the blood. The effective colloid osmotic pressure tending to draw fluid into the capillaries would be 27 cm. of water. Occasionally the protein content of tissue fluid is greatly increased, e. g., when there is lymphatic obstruction, because the lymphatics serve to return protein from the tissue spaces to the veins.[25] Under such circumstances edema formation is greatly facilitated because the effective colloid osmotic pressure in the blood is reduced by the high colloid osmotic pressure of tissue fluid. However, this factor is not important in the edema of congestive heart failure.

Tissue Pressure. The extracapillary tissues themselves exert a force which resists their distention by fluid. This force is known as tissue pressure. It partially counteracts the capillary hydrostatic pressure and thus resists the formation of edema.[61, 107] Normally this measures about 3 or 4 cm. of water and is greater in the lower extremity than in the upper.[12, 92] Low tissue pressure in certain sites, such as in the loose tissue of the eyelids, promotes the accumulation of fluid there. A reduction of tissue pressure in cachectic and bedridden patients with lax subcutaneous tissues and in those whose tissues have been stretched by previous episodes of edema predisposes to the accumulation of edema. Such a reduction in tissue pressure probably exists in inactive or bedridden cardiac patients, but at most it is an accessory factor in the development of cardiac edema.

Lymphatic Drainage. Normally the lymphatics are concerned in the removal of tissue fluid and especially of the tissue proteins which have seeped through the capillary wall. In patients with cardiac edema this lymphatic flow is impaired, due perhaps to the elevated venous pressure which prevents lymphatic

emptying into venous channels.[69] It is uncertain whether this is of much importance in cardiac edema, because the protein content of cardiac edema fluid is low whereas edema fluid caused by lymphatic obstruction contains a high concentration of protein.

Capillary Permeability. An increased capillary permeability can be an important factor in producing edema because it permits the escape of proteins with a consequent diminution in the colloid osmotic pressure of the blood and an increase in the colloid osmotic pressure of the tissues. Its importance as a factor in cardiac edema has been variously evaluated. Smirk[96] experimentally elevated the venous pressures of normal persons and of persons with cardiac failure to levels equally in excess of the measured colloid osmotic pressure. Despite the same pressure difference, he observed a greater accumulation of edema fluid in the cardiac patients. He concluded that the capillaries of patients with cardiac failure were more permeable than those of normal persons. The cause of such permeability is suggested by the experiments of Landis[58] who found that capillaries are rendered permeable to protein when deprived of oxygen for three minutes. Anoxemia of the capillaries with right-sided heart failure is assumed to result from prolonged peripheral stasis. Increased permeability in anoxemic capillaries may also be due to vasodilatation with consequent augmentation of the filtering surface.

Despite these experimental studies and theoretical considerations, clinical observations indicate that the factor of increased capillary permeability is not significant in causing cardiac edema. In many patients with cardiac edema the oxygen saturation of the blood is normal or only slightly reduced. Conversely there is usually no edema in cyanotic patients with congenital heart disease or advanced emphysema despite a low oxygen saturation. The degree of anoxia represented by Landis'[58] experiments is rarely attained in congestive heart failure. The most important objection to the theory of capillary permeability is the low content of protein (0.2 to 0.5 per cent) in edema fluid.[8, 103] Nor is there any change before or after compensation. This indicates that there is relatively little increase in capillary permeability, an increase which is of only secondary importance in causing cardiac subcutaneous edema. On the other hand varying degrees of permeability in different regions of the body may account for the predominant distributions of capillary transudations, e. g., the relative intensities of subcutaneous edema and ascites (see p. 122).

Hormones. It is known that the pituitary antidiuretic hormone is important in controlling water balance, but little is known of any possible relation to cardiac edema.[38] The anterior pituitary and adrenal cortical hormones have also been implicated in the production of cardiac edema.[101, 87] The production of edema by the administration of desoxycorticosterone and salt to patients with Addison's disease has been noted. The possible role of the adrenal cortical hormone in the renal retention of sodium in patients with heart failure has been discussed (p. 96).

PATHOGENESIS OF CARDIAC HYDROTHORAX

The accumulation of fluid in the pleural cavities (hydrothorax) in the course of congestive heart failure is due to the same factors which cause subcutaneous edema. The factor of increased capillary permeability is relatively more important in the development of hydrothorax than as a cause of anasarca, as seen from the higher content of protein in the pleural fluid (2 to 3 per cent

instead of 0.2 to 0.5 per cent). Despite the greater permeability of the pleural capillaries, hydrothorax occurs less commonly than subcutaneous edema, probably because the pleural vessels drain into both the systemic circulation (by way of the azygos veins and the superior vena cava) and into the pulmonary circulation (by way of the pulmonary veins). Thus any tendency to elevation of the pressure within the pleural capillaries because of an elevated venous pressure in one of the circulations (isolated right-sided or isolated left-sided heart failure) is compensated by a free drainage into the other system. Hydrothorax is most often seen in cases of combined right- and left-sided heart failure in which there is back pressure in the pleural capillaries due to venous engorgement in both circulations. On the other hand, hydrothorax appears to arise chiefly as a transudate of the visceral pleura, the venous return of which empties almost entirely into the pulmonary veins. Accordingly, hydrothorax is occasionally a feature also of pure left-sided heart failure with pulmonary congestion.[111]

There is no generally accepted nor completely satisfactory explanation for the occurrence of hydrothorax more frequently on the right side than on the left. The classic explanation held that with enlargement of the right side of the heart the vena azygos major was compressed against the root of the right lung. But the anatomical studies of Fetterolf and Landis[33] indicated that such compression is extremely unlikely. These observers believed that left-sided effusions result from compression of the left pulmonary veins by a large left auricle, and right-sided effusions from compression of the right pulmonary veins by a large right auricle. Dock[21] explained the preponderance of right hydrothorax by the fact that most patients with congestive heart failure assume the right decubitus position, in which the return from the right lung through the right pulmonary vein must be lifted 10 cm. against gravity to reach the left ventricle, while that from the left lung must be elevated only 5 cm.; consequently there is greater venous stasis in the right lung.

Bedford and Lovibond[5] believe that the elevation of venous pressure in the *pulmonary* circulation is of major importance in the production of hydrothorax. The fluid is interpreted as a transudation from the capillaries of the visceral pleura which drain into the pulmonary veins. They support this concept by the fact that the interlobar effusions sometimes seen in left-sided heart failure could only occur as a result of pulmonary capillary venous obstruction since the interlobar pleura is entirely visceral. Bedford and Lovibond found that in cases of isolated left-sided heart failure with regular rhythm left hydrothorax was more frequent than right hydrothorax. On the other hand, right hydrothorax occurred more frequently in the presence of right-sided heart failure and auricular fibrillation. These interesting observations are at variance with the more recent studies of McPeak and Levine,[72] who found that right hydrothorax predominated over left hydrothorax regardless of the underlying cardiac condition. It should be emphasized that bilateral hydrothorax occurs more frequently than unilateral, but even in the former the larger effusion is usually located in the right pleural cavity. Attention is also directed to the frequency of pleural effusions (exudates) in congestive heart failure as a result of pulmonary infarction.

PATHOGENESIS OF ASCITES

Ascites, like the transudate in the pleural cavities, is due fundamentally to the increased venous pressure which accompanies right-sided heart failure.

Here too, however, increased permeability is relatively more important than in the formation of edema, because, as Salvesen and Linder[93] have shown, the ascitic fluid contains 2 to 3 per cent of protein as compared with less than 0.5 per cent in edema fluid. Despite this, ascites occurs less often than subcutaneous edema and later in the course of congestive heart failure.

The greater permeability of the peritoneal capillaries is usually more than offset by the higher pressure in the subcutaneous capillaries, especially in the lower extremities. Since patients with cardiac edema often move about while in the early stages of right-sided heart failure, the factor of gravity causes a greater elevation of venous pressure in the tissues of the lower extremities than in the venules of the peritoneum. Even later, when the patient sits in a chair or at the side of his bed or propped up in bed because of orthopnea, there is a relatively greater capillary hydrostatic pressure in the lower extremities than in the peritoneum.

Ascites is especially prominent and often occurs earlier than overt subcutaneous edema in heart failure associated with constrictive pericarditis or tricuspid stenosis. In these cases hepatic congestion is especially intense and cardiac cirrhosis not uncommon. These observations suggest that the relative degree of hypertension of the portal circulation is a determining factor in the occurrence and prominence of ascites.

PATHOGENESIS OF CYANOSIS

The blue coloration of the skin, which cyanosis signifies, is due to the reduced hemoglobin of the blood. The intensity of cyanosis depends on (1) the amount of reduced hemoglobin in the blood and (2) the amount of blood visible in the superficial vessels of the skin.

The Amount of Reduced Hemoglobin in the Blood

The studies of Lundsgaard and Van Slyke[67] revealed that cyanosis usually appears when the amount of reduced hemoglobin in the blood exceeds 5 gm. per 100 cc. The concentration of reduced hemoglobin in the blood depends on the total amount of hemoglobin in the blood and the percentage of the latter which is uncombined with oxygen.

Total Hemoglobin Content. Normally there are about 15 gm. of hemoglobin per 100 cc. of blood. Cyanosis occurs if one third or more of this is uncombined with oxygen (5 gm. or more per 100 cc. of reduced hemoglobin), i. e., if there is less than 66⅔ per cent oxygen saturation of the blood in the superficial vessels of the skin. In patients with polycythemia, whose total hemoglobin is 20 gm. per 100 cc., cyanosis would appear even if the oxygen saturation were 75 per cent (25 per cent unsaturation of 20 gm. = 5 gm. reduced hemoglobin). On the other hand, extreme oxygen unsaturation is necessary to produce cyanosis in anemic patients. If the total hemoglobin content is less than 33 per cent of normal (i. e., less than 5 gm. per 100 cc.), cyanosis cannot occur even if there is complete oxygen unsaturation, i. e., even if all the hemoglobin is in the reduced form.

Degree of Oxygen Unsaturation. Since 1 gm. of hemoglobin is capable of combining with 1.33 cc. of oxygen, the blood with a normal hemoglobin content (15 gm. per 100 cc.) has an oxygen capacity of 20 volumes per cent. Actually the arterial blood (i. e., after pulmonary oxygenation) contains 19+ volumes per cent of oxygen or is 95+ per cent saturated. This means that there is 1 volume per cent of oxygen unsaturation of the arterial blood. In

passing through the tissues the blood loses an additional 5 volumes per cent of oxygen so that the venous blood has an oxygen unsaturation of 6 volumes per cent. While the loss of oxygen in the capillaries is uneven, we may consider the average of the arterial and venous oxygen unsaturation $\frac{1 \text{ vol.} + 6 \text{ vol.}}{2} \left(= 3\frac{1}{2} \text{ volumes per cent} \right)$ as representing the average oxygen unsaturation of the capillary blood in the skin. Cyanosis occurs with normal total hemoglobin content when the capillary oxygen unsaturation exceeds 6½ to 7 volumes per cent; this represents 5 gm. of reduced hemoglobin.

This degree of oxygen unsaturation may be due to (1) inadequate pulmonary oxygenation of the blood, (2) excessive loss of oxygen from the capillary blood in the tissues or (3) mixing of venous and arterial blood due to a congenital cardiovascular deformity.

Cyanosis due to inadequate pulmonary oxygenation is encountered in cases of severe emphysema, kyphoscoliosis with pulmonary atelectasis, pulmonary fibrosis, extensive pulmonary embolization and other pulmonary diseases which cause a strain on the right side of the heart (cor pulmonale). Cyanosis in such cases of heart disease may occur in the absence of heart failure. Cases of congenital heart disease with pulmonary stenosis and right-to-left shunt may also be included under this category. Relief of cyanosis, among other benefits, results from surgical procedures which increase the flow of blood through the lungs (p. 656).

Mild cyanosis is common in mitral stenosis in which pulmonary congestion of long duration leads to extensive fibrosis of the lung with consequent interference with oxygenation. In patients with left ventricular failure there is usually no significant arterial anoxemia unless there is associated pulmonary edema, pneumonia or other pulmonary complications which may cause cyanosis. When cyanosis is present in patients with right-sided heart failure, it is due either to the pulmonary lesions mentioned or to the associated pulmonary congestion of left-sided heart failure. Oxygen therapy relieves or dispels cyanosis only to the extent that it is due to inadequate pulmonary oxygenation.

Increased deoxygenation of the capillary blood contributes to cyanosis in patients with right-sided heart failure. It is due chiefly to slowing of the blood flow in the tissue capillaries. Cyanosis may occur even with normal pulmonary oxygenation, e. g. if 13 volumes per cent of oxygen are extracted from the capillary blood instead of the normal 5 volumes. For then the average capillary oxygen unsaturation would be $\frac{1 + 14}{2} = 7\frac{1}{2}$. Often there is a combination of inadequate pulmonary oxygenation and increased capillary deoxygenation. In patients with diminished cardiac output, especially those with acute circulatory failure, cyanosis is usually due entirely to capillary deoxygenation, for the arterial blood has a normal oxygen content.

Cardiovascular Shunts. Capillary anoxemia sufficient to cause cyanosis may occur despite normal pulmonary oxygenation and normal capillary deoxygenation when an abnormal cardiovascular shunt causes a significant mixing of venous and arterial blood. This occurs in patients with congenital cardiac malformations (p. 638) such as the tetralogy of Fallot, septal defects or transpositions of the great vessels. Lundsgaard and Van Slyke[67] calculated that in the absence of other abnormalities cyanosis occurs if the amount of venous arterial shunt is more than about 38 per cent of the total cardiac output. Less than this

is necessary if, as is usual, there is an associated polycythemia, or if pulmonary or peripheral stasis due to cardiac failure contributes to the oxygen unsaturation of the blood. In many patients with congenital cardiac deformities the higher pressure in the left side of the heart, as compared with the right, directs the blood from the arterial to the venous side of the shunt. But as a result of exercise, pneumonia, progressive right ventricular hypertrophy or congestive heart failure, the pressure on the right side of the heart may be elevated sufficiently to produce a venous arterial shunt with the consequent development of cyanosis.

The Amount of Blood Visible in the Vessels of the Skin

The intensity of cyanosis depends on the amount of reduced hemoglobin in the blood actually visible through the skin. Therefore, cyanosis is most readily observed where the overlying skin is very thin, e. g., the nail beds, the lips, the tip of the nose, the cheekbones and the ears. Cyanosis is more intense the more blood, and therefore the more reduced hemoglobin, is actually in the vessels of the skin. This in turn is greater the more numerous and the more dilated are the capillaries and venules of the skin.

The state of the subpapillary venous plexus is much more important in causing cyanosis than that of the superficial capillary loops, for the former presents a greater area parallel to the skin. Mechanical distention of the subpapillary venules in healthy persons by compression of the arm veins can produce cyanosis even though there is a normal oxygen saturation; for although the amount of reduced hemoglobin is not elevated, the amount visible is greatly increased. In patients with congestive heart failure, similar distention of the subpapillary venules is caused by the elevated venous pressure.

Factors Modifying Cyanotic Hue

The blue color of the skin in cyanotic patients with heart disease may vary in hue and intensity. In patients with polycythemia the skin is purple or reddish blue because there is an increase in the red of the oxyhemoglobin as well as in the blue of reduced hemoglobin. A pale ashen or leaden type of cyanosis is seen when the superficial cutaneous vessels are constricted and relatively empty of blood. This is seen in patients with acute circulatory failure or whenever there is a sharp reduction in the cardiac output. The cyanosis is then due to the reduced hemoglobin in the less visible deeper venous plexus below the skin. In patients with tricuspid valvular disease and heart failure the blue of cyanosis is often mingled with the yellow color due to icterus.

PATHOGENESIS OF ICTERUS IN HEART DISEASE

Jaundice is due to an excessive amount of bilirubin in the blood serum. While hyperbilirubinemia is present in many patients with congestive heart failure, it is sufficient to produce jaundice only in about 4 per cent of them, most often in those with combined mitral and tricuspid valvular disease.[57] The significant clinical features of these cases with jaundice are severe and long-standing passive congestion of the lungs and the liver, and the great frequency of pulmonary infarction.[52, 90]

There is evidence that the hyperbilirubinemia is due to impairment of liver function. This is indicated not only by the hyperbilirubinemia itself but also by the increase in urobilinogen in the urine and by the bromsulfalein test of

hepatic function.[49] However, in the presence of heart failure there is uncertainty as to the interpretation of the latter test.[6a] In patients with frank jaundice associated with heart failure there is a prompt and direct van den Bergh reaction, but more often patients with heart failure have a slight hyperbilirubinemia and an indirect van den Bergh reaction. The impairment of liver function may be due to oxygen deficiency, and this in turn is caused partly by prolonged stasis of blood in the congested liver and partly by deficient pulmonary aeration in consequence of extensive pulmonary infarction. Clinical observations suggest that jaundice and presumably hepatic damage in congestive heart failure are correlated with *very* high venous pressure and prolonged duration of the latter.

Hyperbilirubinemia and jaundice are caused to some extent also by excessive production of bilirubin, for there is an increased quantity of urobilin in the stools as well as of urobilinogen in the urine. The increase in formation of bilirubin may result from excessive destruction of blood in the lung, the blood representing either infarcted areas or the red blood cells extravasated in the pulmonary alveoli. Evidence of increased destruction of blood is seen clinically in the expectoration of heart failure cells and at necropsy in the deposition of hemosiderin, the brown iron pigment, within the lung (brown induration). While pulmonary infarction thus plays an important role in causing jaundice both by producing arterial anoxemia and by increasing the formation of bilirubin, it is not an essential factor, as jaundice in patients with heart failure may occur in its absence.

PATHOGENESIS OF GALLOP RHYTHM

There are three main types of gallop rhythm: (1) the protodiastolic, (2) the presystolic and (3) summation gallop. In addition there are instances in which an extra sound of uncertain origin occurs during systole. This has been termed systolic gallop or systolic click, but its mechanism and significance differ greatly from the usual forms of gallop rhythm.

Protodiastolic Gallop Rhythm. This occurs early in diastole during the phase of rapid diastolic filling of the ventricle. It coincides in time with the occurrence of the third heart sound, i. e., about 0.16 to 0.2 second after the second heart sound.[10] In fact the protodiastolic gallop is most generally believed to represent an accentuated third heart sound[62, 108] and to be due to a similar mechanism.[31, 98]

Protodiastolic gallop occurs in left ventricular failure and is believed to result from the very rapid inflow of blood, during early diastole, into a dilated, flabby left ventricle. The sound is caused by the resulting vibrations of the ventricular wall, by its impact on the surrounding tissues and chest wall,[108] or less likely by vibrations of the mitral valve.[64] The high pulmonary venous and left atrial filling pressure in left heart failure and acceleration of the heart rate are factors which intensify the phase of rapid ventricular filling and predispose to protodiastolic gallop. This is the type of gallop which occasionally occurs with auricular fibrillation, since it is not dependent on auricular contraction.

A distinct third heart sound resembling protodiastolic gallop is heard occasionally in children and young adults. But a protodiastolic murmur after the age of thirty is usually due to left ventricular failure, or less commonly to right ventricular failure. Associated evidence of cardiac disease and left ven-

tricular failure supports the interpretation of a gallop rhythm rather than of a normal third heart sound. According to Bramwell,[9] a third heart sound, unlike gallop rhythm, is not palpable and may be heard at normal cardiac rates.

Presystolic Gallop Rhythm. The gallop sound occurs just prior to the first heart sound, but is separated by at least 0.08 second. It coincides with auricular systole and is believed to represent an accentuated auricular sound.[62, 82, 78] The auricular origin of this type of gallop sound is supported by its disappearance or failure to occur in the presence of auricular fibrillation.

When the P-R interval is prolonged or when there is very pronounced tachycardia, the auricular gallop sound is displaced in the shortened diastole and it may be mesodiastolic or protodiastolic. The presystolic murmur of mitral stenosis, the opening click of the mitral valve and an audible auricular sound when there is tachycardia and a prolonged P-R interval may have to be differentiated from gallop rhythm. Phonocardiographic tracings are often necessary. The Austin Flint murmur (p. 594) has been interpreted as presystolic gallop rhythm.[62]

Summation Gallop. This is the most common form of gallop rhythm, and results from the coincidence of the third heart sound and the auricular sound or of protodiastolic and presystolic gallop sounds. Prolongation of the P-R interval and pronounced tachycardia are responsible for this coincidence. Summation gallop may occur as a result of left or right ventricular failure combined with tachycardia, but also occurs in normal persons with tachycardia or in patients with rheumatic fever, who exhibit tachycardia and a prolonged P-R interval.

Systolic Gallop. The extra or "gallop" sound is heard between the first and second sounds, most often at the base of the heart and occasionally at the apex.[84, 109] It may be due to vibrations set up in a dilated aorta or to pleuropericardial adhesions,[4a] but its mechanism is uncertain. It is of doubtful clinical significance and has been observed in "nervous" individuals and in those with infectious diseases.[100]

PATHOGENESIS OF PULSUS ALTERNANS

(Alternation of Pulse; Cardiac Alternans)

Pulsus alternans is an evenly spaced alternation of strong and weak cardiac or pulse beats. It occurs most frequently in cases of left ventricular failure, especially those due to hypertension or coronary arteriosclerosis, but it has been observed also in association with auricular or ventricular tachycardia. Electrical alternans,[51] which refers to alternation in size of the QRS or T complexes, occurs in these conditions and also as a result of digitalis intoxication.[50, 20]

Pulsus alternans is distinguished from the sequence of strong and weak beats of pulsus bigeminus (p. 248) by the fact that the weak beat in pulsus alternans is very slightly closer to the succeeding beat than to the preceding. The weak premature beat of pulsus bigeminus is distinctly closer to the preceding normal beat.

A detailed discussion of the pathogenesis of pulsus alternans may be found in the monographs of Poumaillaux[85] and of Kisch.[54]

The alternation in pulse is most generally attributed to a corresponding alternation in the strength of ventricular contraction, and therefore in the amount of blood ejected into the peripheral arteries. The interval between

beats is approximately unchanged, but the weak beat is slightly delayed due to slower transmission of the pulse wave. In the electrocardiogram the cycle lengths are equal. The alternation in strength of cardiac contraction is believed to be due to disease or fatigue of many cardiac fibers, as a result of which there is a variation in excitability or refractoriness. During the strong beat most of the fibers respond, but the others are refractory; during the weak beat fewer fibers contract, including those which were previously refractory.[40, 77, 7]

Of interest is the observation that pulsus alternans may be initiated by a premature beat, usually in cases with tachycardia in which the diastolic period is shortened. The premature beat further shortens the brief diastole and significantly reduces the degree of filling and leaves many fibers refractory. The subsequent compensatory pause permits greater filling and myocardial recovery. Thus an alternating pattern of contraction may be initiated. When associated with a tachycardia but without organic disease, pulsus alternans is usually relatively benign, in contrast with its serious prognostic implication in cases of left-sided heart failure.

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8

CIRCULATORY MEASUREMENTS IN CONGESTIVE HEART FAILURE

THE CARDIAC OUTPUT

The cardiac output is the effective volume of blood expelled by either ventricle of the heart in a unit of time. This is expressed as cubic centimeters or liters per minute. The output of the two ventricles is usually identical, for the weaker musculature of the right ventricle is counterbalanced by the lesser resistance against which it works. If there is a regurgitation of blood due to aortic valvular insufficiency or a shunting of blood due to congenital defects, the actual output of the heart may be greater than the effective output. The volume of the circulation, the minute volume and the rate of circulation are used synonymously with cardiac output. I prefer the latter term because of its more common usage and because the other terms may be confused with blood volume and circulation rate. The output of each ventricle per beat is known as the stroke output and ranges between 60 and 100 cc., with an average of 75 cc. when the heart rate is 72 per minute. The cardiac output is equal to the stroke output multiplied by the cardiac rate. Thus an increase in cardiac output may be effected by an increased stroke output, an increased cardiac rate or both.

Measurement of the Cardiac Output

The cardiac output may be determined by:

(1) Direct application of the Fick principle.
(2) Indirect application of the Fick principle.
(3) Dilution methods, including use of foreign gases and dyes.
(4) Physical methods.

The Fick Principle. Fick[43] pointed out that the amount of blood traversing the pulmonary capillaries in a unit of time is a measure of the cardiac output (from the right ventricle). Since the diffusion of oxygen or carbon dioxide across the pulmonary alveolar walls depends on the pulmonary blood flow, the latter can be determined from the amount of oxygen absorbed in a unit of time and the difference in oxygen concentration of the blood before and after leaving the lungs, i. e., the arteriovenous oxygen difference. It is assumed that the amount of oxidation in the lungs is negligible. Thus if the oxygen concentration of the arterial blood is 190 cc. per liter and that of the venous blood 150 cc. per liter, each liter of blood absorbs 40 cc. of oxygen. If 200 cc. of

oxygen are absorbed by the subject in one minute, $\frac{200}{40}$ or 5 liters of blood must have flowed through the lungs in a minute in order to absorb this quantity of oxygen. This pulmonary blood flow is the right ventricular output, which is presumed to equal the left ventricular or cardiac output.

Expressed mathematically:

$$\text{Cardiac Output (liters per min.)} = \frac{\text{Total oxygen absorption (cc. per min.)}}{\text{Arterial oxygen} - \text{mixed venous oxygen (cc. per liter)}}$$

The cardiac output may be similarly calculated from the total carbon dioxide elimination in a unit of time and the arteriovenous carbon dioxide difference.

$$\text{Cardiac Output (liters per min.)} = \frac{\text{CO}_2 \text{ elimination (cc. per min.)}}{\text{Venous CO}_2 - \text{arterial CO}_2 \text{ (cc. per liter)}}$$

It may be seen from the above equations that while the cardiac output tends to increase with an increase in oxygen absorption the cardiac output may actually diminish, despite increased oxygen absorption, if the arteriovenous oxygen difference is increased to an even greater extent. Thus in some cases of cardiac failure associated with circulatory stasis, slowing of the blood stream may lead to the abstraction of 7 to 10 volumes per cent of oxygen by the tissues instead of the normal 4 to 5 volumes, with a concomitant reduction in cardiac output even though the patient's metabolism (and total oxygen absorption) is elevated.

The Direct Fick Method. (a) *The oxygen absorption* in cc. per minute under basal conditions is determined with the aid of a basal metabolism machine (such as the Benedict-Roth apparatus). For comparative cardiac outputs, e. g., before and after exercise, the oxygen consumption can be determined from 2 or 3 minute samples of expired air collected in Douglas bags, analyzed in an Haldane apparatus, and measured in a Tissot spirometer.

(b) The *oxygen content of arterial blood* is found by direct puncture of a convenient artery such as the brachial, radial or femoral. An indwelling needle permits repeated sampling if multiple cardiac outputs are to be determined during a period of study. The arterial blood is collected under oil in heparinized syringes, stored promptly in ice and the oxygen content determined as rapidly as possible by the manometric method of Van Slyke and Neill[155] or by the micromethod of Roughton and Scholander.[143]

(c) The *oxygen content of mixed venous blood* can now be satisfactorily determined from blood samples obtained by intracardiac catheterization.[47, 94, 27, 115, 29]

A very flexible radiopaque catheter, provided with a slight curve on its distal 8 cm., is introduced by way of the median basilic vein (or the saphenous vein in children) after cutting down on the vein with the aid of procaine. A flow of saline (with 1 cc. heparin per 1000 cc. saline) is maintained through the catheter at a rate of about 50 cc. per hour to prevent clotting. By rotation of the tip and observation under fluoroscopy the catheter can be successively passed into the superior vena cava, right atrium, right ventricle and pulmonary artery, as well as into the inferior vena cava or hepatic or renal vein, occasion-

ally into the coronary sinus and occasionally into other cardiac chambers or great vessels when shunts exist. The position of the catheter, at the times when blood samples are taken, can be checked by spot x-ray films and by pressure measurements with the aid of a Hamilton or strain gauge manometer.

For mixed venous blood, satisfactory specimens in hearts without shunts are best obtained from the pulmonary artery or right ventricle. Complete mixing may not occur in the right atrium because of independent laminar flow of blood from the superior and inferior vena cava which may differ in oxygen concentration, or because of proximity to the coronary sinus, the blood from which is much lower in oxygen content than mixed venous blood. Several specimens should be taken from various parts of the chamber and they should not differ by more than 0.5 volumes per cent if they represent mixed venous blood. The oxygen determinations are made as on arterial blood.

The cardiac output is then determined by substituting the values obtained in the Fick formula:

$$\text{C. O.} = \frac{O_2}{\text{a–v oxygen difference}}$$

There is no serious criticism of the accuracy of the direct Fick method if the technic is properly carried out by a trained team and if every effort is made to keep the patient in a physiologic state.[158] However, the technical requirements make this method impractical for general clinical usage. Recently a new method has been proposed for the direct measurement of the arteriovenous oxygen difference with the aid of a photoelectric colorimeter.[85b] If its accuracy is confirmed, it would simplify the use of the Fick principle for determining the cardiac output.

Indirect Fick Methods. These methods, based on the Fick principle, are designed to avoid the necessity of puncturing an artery or of catheterizing the heart to obtain mixed venous blood.

The oxygen consumption is determined as above.

The arterial content of oxygen (or of carbon dioxide) is calculated from determinations of the alveolar tension of oxygen (or carbon dioxide). The sample of alveolar air is obtained by forced expiration into a Haldane tube with a sampling bulb attached.

The oxygen or carbon dioxide content of mixed venous blood is calculated from analysis of a sample of air obtained by having the subject rebreathe into a large rubber bag until the air is in equilibrium with mixed venous blood.[33]

The values obtained are substituted in the Fick formula (supra).

The reported cardiac outputs obtained by these means are variable, due probably to incomplete mixing, with consequent high outputs when the rebreathing time is short, and to recirculation of the blood, with consequent low cardiac outputs if the rebreathing time is too long (more than 10 to 15 seconds).

Dilution Methods. A measured amount of foreign gas is inhaled or a dye or other substance is injected intravenously. The amount of blood flow in unit time required to absorb the measured uptake of gas or intravenously injected material represents the cardiac output.

Foreign Gases. The methods employing *nitrous oxide* have been described in detail by Krogh and Lindhard[98] and by Lindhard,[107] the use of *ethyl iodide* by Henderson and Haggard[71] and by Starr and Gamble,[148] and that of *acetylene*

by Marshall and Grollman[111] and by Grollman.[64] Acetylene has been most widely used until recently because it was found to be an inert, readily diffusible gas which did not combine with lipoids or other constituents of the blood and was easily analyzed.

The foreign gas methods, and specifically the acetylene method, have been criticized by Hamilton.[69] The chief error lies in the rebreathing procedure. It is probable that in the nitrous oxide and acetylene procedures, recirculation occurs and induces underestimation of the pulmonary blood flow during the test period. Gladstone[57] obtained higher normal cardiac outputs than Grollman[64] by limiting the rebreathing period to 12 seconds; Gladstone's[57] curves of acetylene disappearance suggested that after this interval recirculation of the blood occurred.

Intravenous Injection of Dyes. Hamilton and his co-workers[70] have determined the cardiac output by means of the rapid intravenous injection of brilliant vital red followed by the prompt withdrawal of repeated samples of blood from the femoral artery. The samples of arterial blood are analyzed colorimetrically for dye. These values are plotted as ordinates on semi-logarithmic paper with time in seconds as the abscissa. The time of recirculation is marked clearly by a sudden change in the direction of the concentration curve thus obtained.

From the concentration curve the time of one circulation and the average concentration of the dye in that circulation are determined. Since the quantity of dye injected is known, and the time of the first circulation and the average dye concentration are determined by the procedure, the cardiac output can be calculated as follows:

$$\text{C.O.} = \frac{60 \times \text{I}}{\text{C T}}$$

in which C.O. is the cardiac output, I is the quantity of dye injected, C is the average dye concentration in one circulation and T is the duration of one circulation in seconds.

Although the underlying assumptions of this method have been questioned, the values obtained check satisfactorily with those determined by the direct Fick method. The need for multiple arterial punctures and the laborious calculations limit its practical usefulness.

Electrical Conductivity Method. A measured amount of salt solution may be rapidly injected into a vein and the cardiac output may be calculated as for dye, if the average concentration of the salt solution during one circulation can be determined by measuring its electrical conductivity.[164, 85a] Changes in conductivity in the blood of a cannularized artery, measured by an electronic device and continuously recorded against time, produce a time-concentration curve of the injected conducting solution. From this, the time of one circulation and the average concentration of the conducting solution during that period can be determined. Technical difficulties are still to be overcome.

Physical Methods. Physical methods of determining the cardiac output have the advantage of avoiding the necessity of arterial or venous punctures or of chemical determinations. However, none of the methods employed have thus far provided uniformly accurate absolute values of cardiac output. In general the calculations are standardized by comparison with the direct Fick procedure. Hamilton[69] has given a detailed criticism of these methods.

Three physical methods have been used in humans: (1) X-ray measurements; (2) pulse pressure and pulse wave measurements; (3) ballistocardiography.

X-ray Measurement of Cardiac Output. The volume of the heart is determined roentgenographically in maximum systole and diastole by synchronization of the roentgen ray machine with an electrocardiograph. The surface areas are measured with a planimeter and the volumes calculated therefrom by the use of Bardeen's formula.[8] The combined cardiac output of the two ventricles is equal to the difference between the calculated systolic and diastolic volumes (stroke output) multiplied by the number of cardiac contractions per minute. This value must be divided by 2 to obtain the cardiac output as usually defined, i. e., the output of either ventricle.[41, 116, 106]

Similar roentgenological determinations of the cardiac output have been made with the aid of the kymograph.[87, 93] The outputs determined by these examinations have been too low, probably because the roentgen ray films do not disclose all of the pulsation of the heart responsible for the ejection of blood.

Pulse Wave and Pulse Pressure Measurements. This physical method is based on the premise that the cardiac output varies approximately as the product of the pulse pressure, the arterial distensibility and the cardiac rate.[37] The distensibility of the arterial system is determined from the pulse wave velocity and the diameter of the aorta.

A variety of formulae have been proposed for calculating the cardiac output, those of Frank,[48] Broemser and Ranke,[18] Böger and Wezler,[16] and Bazett et al.[9] being the best known. Böger and Wezler[16] advocated the following formula for calculating the stroke output:

$$\text{S.O.} = \frac{2Q \times \triangle P \times L}{ga^2}$$

in which Q is the diameter of the aorta, $\triangle P$ is the pulse pressure, L is the length of the arterial compression chamber receiving blood during systole, g is the specific gravity of blood and a is the pulse wave velocity in cm. per second. Simultaneous subclavian and radial pulse tracings are made from which the pulse wave velocity and L can be determined. The diameter of the aorta is estimated from roentgenograms or is taken from statistical tables based on postmortem studies.

The results obtained with these methods are of dubious reliability even though they are of value in comparative determinations in the same subject. Often empiric modification of the calculated outputs are necessary to bring them in alignment with determinations of the cardiac output by gasometric or direct Fick procedures. Considerable experience and meticulous care are necessary in the registration of the pulse waves and in the analysis and measurement of the curves obtained. The measurements of aortic diameters based on postmortem studies are considerably below actual values during life.

Ballistocardiograph. The ballistocardiograph is an instrument which registers graphically the recoil of the heart and body and the impacts of the ejected blood.[149] The subject lies on a fixed bed or table or stands on a platform in contact with a spring-like device to which the recoil of the body is transmitted. The motions of this pick-up device are greatly magnified optically and photographed. The machine is calibrated by determining the force necessary to

deflect the recording light beam 1 cm. Starr and associates[149] have used an apparatus of high frequency (15 per second) without damping, while Nickerson and Curtis[129] have devised a low frequency (1.5 per second) critically damped ballistocardiograph. Cardiac outputs determined with the high-frequency, undamped, and with the low-frequency damped ballistocardiograph have checked satisfactorily with determinations made by right heart catheterization and the Fick principle.[28, 158] The ballistocardiograph is of particular value in determining rapid changes in output in the same subject. The results are unsatisfactory in cases with output regurgitation, as in aortic insufficiency, in patients with arrhythmias or respiratory distress, in subjects who cannot hold their breath for a few seconds, and in those with pronounced tremor.

The premise upon which the use of the ballistocardiograph for determining cardiac output is based has been criticized.[69] The calculated values are inaccurate as absolute measures of the stroke output and must be modified empirically by comparison with the direct Fick method. According to Cournand, Ranges and Riley[28] a considerable error is due to underestimation of the true diameter of the aorta due to the use of tables based on measurements after death. They found that the ballistocardiogram gave results which were 18.5 per cent too low. By measuring the diameter of the aorta after diodrast visualization, they obtained values for the cardiac output which corresponded closely to that obtained by the direct Fick procedure. Nickerson et al.[130] also observed a good correlation between ballistocardiograph and direct Fick determinations of the cardiac output in 47 subjects.

Despite these shortcomings the ballistocardiograph is finding increasing application in clinical research. It is especially useful for comparative measurements of stroke output in the same individual and for determining patterns of abnormal cardiovascular function. Because the subject must be quiet during the recording, the ballistocardiograph cannot be used to determine the cardiac output during exercise.

The Cardiac Output in Health and Disease

The cardiac output under basal conditions (i. e., with the body recumbent, at rest, at least twelve hours postprandially and in a room at 20° C.) varies between 4 and 7 liters, with an average of 5.3 liters.[29, 115, 150] These values were obtained with the direct Fick method and cardiac catheterization, but similar values had previously been obtained by Henderson and Haggard[71] with the ethyl iodide method and by Hamilton et al.[70] by the intravenous dye dilution method. The corresponding stroke outputs average between 70 and 80 cc.

These values are about 30 per cent higher than those obtained with the acetylene method by Grollman.[64, 23a] Presumably the latter determinations yielded too low values because of recirculation of the blood, especially through the coronary system, during the relatively long period of rebreathing (23 seconds).

The normal value for cardiac output is more constant when expressed in terms of the surface area and averages 3.2 liters per square meter. It is somewhat higher in children. The minute cardiac output per square meter is known as the *cardiac index*.

The percentage of the cardiac output distributed to individual organs varies with their needs at any given moment. When the requirements of an organ

increase, its arterioles open in response to the local accumulation of metabolic waste products, or to local or axone reflexes, and more of the cardiac output of blood flows to that organ. With reduced activity, a reversal of these mechanisms causes arteriolar constriction and a diminution of blood flow.

Determinations of the blood flow to various organs have yielded the following results:

Renal blood flow	1.3 liters per minute[157, 24]
Cerebral blood flow	0.8 liters per minute[92]
Extremities	1.8 liters per minute[1]
Hepatic blood flow (including viscera drained by portal vein)	1.3 to 1.5 liters per minute[17, 125]

The cardiac output is less when the subject is upright than when he is recumbent,[115] probably due to the diminished venous return to the heart in the former position.[128] The cardiac output is also diminished after prolonged standing, on holding the breath in inspiration, and in persons of advanced age. Anxiety may be associated with an elevation in cardiac output.[150]

Pathologic Conditions Associated with a Diminished Cardiac Output

1. Myxedema (p. 932).
2. Constrictive pericarditis (p. 532) and occasionally pericarditis with effusion (p. 507).
3. Paroxysmal tachycardia and auricular fibrillation with rapid ventricular rate—due to the diminished period of diastole and consequent reduction in diastolic filling (Chapter 12).
4. Heart block, occasionally when the increased stroke output is insufficient to compensate for the slow cardiac rate (p. 302).
5. Shock states (Chapter 10).
6. Valvular heart disease, particularly aortic stenosis or mitral stenosis, is occasionally associated with a diminished cardiac output. The cardiac output may be normal when the patient is at rest but increases less than normally with exercise.
7. Congestive heart failure. (This is discussed in detail in Chapter 6.) Usually there is a decrease but the cardiac output may be normal. With exercise there is little or no increase in cardiac output, in contrast with the pronounced augmentation in normal individuals.[72]
8. Auricular fibrillation. Most observers have found the cardiac output diminished by 20 to 30 per cent[91] with a corresponding increase when regular rhythm is reestablished by quinidine.[146] These observations have been criticized by Kohn and Levine.[96]

Increased Cardiac Output

The cardiac output is *increased* most commonly as a result of muscular exercise. Digestion may increase the cardiac output by 30 to 40 per cent one hour after a meal and the increase may persist for three hours. Emotional excitement may produce a similar increase. The increase in cardiac output and consequent increase in the work of the heart may account for the precipitation of attacks of angina pectoris in susceptible patients following exercise, meals or excitement. The cardiac output is increased after the ingestion of fluids and after intravenous infusions in therapeutic doses.[3] Pregnancy is

associated with an elevation of cardiac output varying between 45 and 85 per cent (p. 1017). A rise in environmental temperature to above 30° C. and the initial period of exposure to high altitudes are associated with increased cardiac output.

Pathologic Conditions Associated with Increased Cardiac Output

1. Hyperthyroidism (p. 914).
2. Fever. The increase, as in Graves' disease, is due to the elevated metabolism. The systolic output is unaltered or slightly diminished so that the increased cardiac output corresponds to the rise in heart rate.
3. Anemia (p. 969).
4. Arteriovenous fistula (p. 599).
5. Beriberi (p. 956).
6. Severe pulmonary emphysema.
7. Osteitis deformans.

THE CIRCULATION TIME

The determination of the speed of blood flow is of clinical value because of its distinctive alteration in congestive heart failure and other circulatory disturbances. Clinical methods do not actually measure the velocity of the blood flow, which varies considerably in diverse parts of the vascular tree due to differences in the caliber of arteries, capillaries and veins. The *circulation time* measures the shortest interval between the injection of a substance into a vein and its arrival at some distant site in sufficient concentration to produce a recognizable end point. It represents approximately the inverse of the average velocity of blood flow between two points.

The circulation time is related to both the cardiac output and the volume of the circulating blood. The circulation time tends to increase as the blood volume increases, for the capacity of the vascular tree is enlarged, the average caliber of the vessels widened and the blood stream slowed. The circulation time tends to diminish as the cardiac output increases, for the latter indicates that there is a greater volume of blood passing a given point in a given time. Unless the caliber of the vessel is enlarged, this is possible only if the speed of the circulation is increased. However, the circulation time may remain unchanged if there are simultaneous and similar increases in cardiac output and blood volume. This relationship may be expressed mathematically:

$$CT = k \frac{BV}{CO}$$

in which CT represents the circulation time, BV the circulating blood volume, CO the cardiac output per minute, and k a "constant" which, however, is undetermined and which in fact may vary somewhat in different individuals or even in the same individual under changing conditions. It is apparent from the above formula that the circulation time is most likely to be prolonged if there is both an increase in the blood volume and a diminution in cardiac output, findings typical of advanced congestive heart failure.

Methods of Determining the Circulation Time

The usual technic is to inject rapidly a foreign substance into a peripheral vein and to note the time elapsing between the injection and the arrival of

the substance at some other point in the circulation. Koch[95] first employed fluorescein, but his method was impractical because of the need for multiple venipunctures. Fundamental work on the circulation time was contributed by Blumgart and Weiss.[15] They injected radium C into an antecubital vein and detected its arrival in the right side of the heart (arm-to-right-heart time) and in the opposite antecubital artery (arm-to-arm time) by a special radiosensitive device.

Histamine in a 1:5000 or 1:10,000 solution (0.001 mg. per kilo body weight) has been injected into an antecubital vein and its arrival in the capillaries of the face noted by a distinct flushing which is accompanied simultaneously by a metallic taste on the tongue.[160] The procedure is seldom used because of the frequency of headache, the insufficient color change in Negroes and anemic subjects, a delayed reaction time and occasional serious attacks of acute dyspnea resembling cardiac asthma.

Sodium cyanide, administered in a 2 per cent aqueous solution (0.11 mg. per kilo), when injected into the antecubital vein increases the depth of respiration, presumably by stimulating the carotid sinus. With this method, Robb and Weiss[141] found the arm-to-carotid time to be 9 to 21 seconds (average 15.6 seconds). There is some question as to whether the site of the end point is actually the carotid sinus.[100] Although the method has the advantage of an objective end point (increase in respirations which can be seen and recorded graphically) there are occasional alarming reactions including syncope and respiratory arrest, and the end point may be masked by cardiac dyspnea.

Papaverine likewise causes a sudden deepening of respiration and has been recommended as an objective measure of circulation time by Elek and Solarz.[35] The dose is 40 mg. (1.25 cc.) injected intravenously. The average circulation time is given as 20.8 seconds and the range 15.4 to 27.0.

Alpha lobeline has been similarly employed.[11] The dose is 0.5 cc. of a 1 per cent solution; the end point is a cough usually accompanied by a grimace and hyperpnea.

Clinical Methods. The clinical methods which are used most generally measure the arm-to-tongue time and employ solutions of either decholin, saccharin or calcium gluconate as the injected material. Volatile substances such as ether are often injected intravenously in order to determine the arm-to-lung time. These substances have the disadvantage of producing subjective end points. Consequently, the patient's reaction time and degree of cooperation are factors which may affect the result.

The test is performed with the patient recumbent after having rested at least twenty minutes. He should be reassured so that he is relaxed and his pulse and respiration are basal. In particular, he must be told not to hold his breath after insertion of the needle as this may retard the venous return to the heart. The nature of the end point, such as a sweet or bitter taste, should be explained to the patient as well as the importance of his announcing it *immediately* by some agreed signal such as "now" or "sweet." After the tourniquet is applied and the needle inserted, the tourniquet should be released and 20 to 30 seconds allowed to elapse to permit reestablishment of the normal circulation in the vein before the injection is made. It is essential that the quantity of solution used be small enough, and the bore of the needle large enough (about 18 gauge) to permit *rapid injection* (less than a second). A stop-watch is started at the instant the injection is begun and stopped when

the patient signals the end point or when an objective end point is noted. Whenever possible, the test should be repeated after a few minutes to check the result.

Decholin (sodium dehydrocholate)
Quantity: Five cc. of a 20 per cent solution.
End point: Bitter taste and involuntary grimace.
Normal arm-to-tongue time: 10 to 16 seconds.[153, 50]
Comment: Sharp and usually reliable end point but relatively expensive.

Saccharin (sodium benzosulfimide)
Quantity: 2.5 cc. prepared by dissolving 2.5 gm. of soluble saccharin (Merck) in 2 cc. distilled water and heating *just enough* for solution.
End point: Sweet taste.
Normal arm-to-tongue time: 9 to 16 seconds.[45, 7]
Comment: Cheap. Small volume of solution needed. Local venous thrombosis and painful swelling if perivenous tissue is infiltrated.

Calcium gluconate
Quantity: 3 to 5 cc. of a 20 per cent solution.
End point: Hot sensation in tongue and pharynx.
Normal arm-to-tongue time: 10 to 16 seconds.[58, 156]

Magnesium sulfate
Quantity: 10 cc. of a 10 per cent solution. (Also a mixture of magnesium sulfate and calcium gluconate has been used.[147])
End point: Hot sensation in tongue and pharynx.
Normal arm-to-tongue time: 7 to 17 seconds.[12]

Fluorescein or Riboflavin
Quantity: 2 cc. of a 20 per cent solution of sodium fluorescein *or* 0.8 mg. per kilo body weight of riboflavin.[165]
End point: Greenish-yellow fluorescence in mucous membrane of lips[102] or in previously prepared histamine wheal of arm.[127] Visualized in dark with source of ultraviolet light.
Normal arm-to-lip time: 10 to 16 seconds.
Comment: Objective end points.

Radioactive Sodium
The circulation time may be determined by injecting radioactive sodium (Na^{24}) intravenously and clocking its arrival at any distant point by a Geiger-Mueller counter.[79] By means of special ink-writing counters placed over the precordium, Prinzmetal et al.[140] have recorded curves (radiocardiograms) visualizing the flow of blood through the heart.

Ether
Quantity: 5 minims ether and 10 minims normal saline[73, 120] (1.4 cc. paraldehyde may be substituted).[22]
End point: Facial grimace; cough; ether taste or smell.
Normal arm-to-lung time: 4 to 8 seconds.

Carbon Dioxide
Quantity: Inhale 50 per cent mixture carbon dioxide in air.[65]
End point: Acceleration and deepening of respiration.
Lung-to-carotid sinus time: 5 to 10 seconds.

Nitrogen or Helium
While the oximeter is measuring the arterial oxygen saturation in the ear, the subject inhales a single breath of 100 per cent nitrogen or helium.[34a] The end point is a reduction in arterial oxygen saturation at the site of the oximeter. This measures the lung-to-ear time.[163]

Clinical Abnormalities of the Circulation Time

Diminished Circulation Time. The circulation time is *reduced* in the following pathologic conditions:

1. Hyperthyroidism (p. 915).
2. Anemia (p. 968). The reduction in circulation time with both primary and secondary anemias parallels the severity of the anemia.[153, 58]

3. Beriberi heart disease (p. 956).
4. Arteriovenous fistula (p. 599).
5. Pregnancy (p. 1018).
6. Congenital heart disease (p. 684).
7. Febrile states. Acceleration of the circulation is the result of peripheral vasodilatation.

The circulation time is also reduced during digestion and after exercise. Because of these effects, the circulation time should be determined when the patient is in a basal state.

Prolonged Circulation Time. A *prolongation* of the circulation time is observed in the following pathologic conditions.

1. Congestive heart failure (see below).
2. Polycythemia vera. The slowing of the circulation[14] is dependent on the increase in circulating blood (erythrocyte) volume and the associated increase in viscosity of the blood.
3. Myxedema (p. 933).

The circulation time is normal in cases of compensated valvular heart disease or hypertension. If the circulation time is prolonged in these conditions, careful investigation usually elicits some subjective or objective evidence of cardiac failure.

The Circulation Time in Congestive Heart Failure

A prolonged circulation time most often denotes the presence of congestive heart failure. Extreme degrees of circulatory slowing are found exclusively in this condition. As a rule the circulation time in cases of congestive heart failure varies between 20 and 40 seconds but occasionally it is 50 seconds or more. Most of the circulatory slowing occurs in the pulmonary vessels and in the enlarged cardiac chambers.[126]

In pure left-sided heart failure the circulation time usually exceeds 16 seconds, the delay being due to pulmonary stasis.[76] When exertional dyspnea, asthmatic attacks or orthopnea are associated with a prolonged circulation time, they may usually be assumed to be due to left-sided heart failure. If there is no associated right-sided failure, the arm-to-tongue time may be increased while the arm-to-lung (ether) time is normal. This indicates that the circulatory stasis is confined essentially or exclusively to the venous portion of the pulmonary circulation. Thus by doing both a saccharin (arm-to-tongue) and an ether (arm-to-lung) test and subtracting the result of the latter from that of the former, the circulation time may be subdivided into arm-to-lung and lung-to-tongue time. An increase in the former (above 9 seconds) represents right-sided, and an increase in the latter (above 11 seconds) left-sided heart failure.

In pure right-sided heart failure the arm-to-tongue (saccharin) time and its arm-to-lung (ether) component are prolonged but the lung-to-tongue time may be normal. In combined right- and left-sided heart failure the longest circulation times are encountered. Both the arm-to-lung and lung-to-tongue fractions are increased.

The prolongation of the circulation time is only approximately related to the severity of the patient's symptoms. In patients with left-sided heart failure the circulation time tends to increase as the dyspnea and orthopnea become more intense or when cardiac asthma or pulmonary edema appears. But when the

right ventricle also fails, the patient's respiratory distress may be alleviated although the circulation time increases. Thus patients with cardiac failure whose circulation time is 30 seconds or more may be comfortable when lying flat in bed or even when ambulant. Occasionally patients suffering from attacks of cardiac asthma have a long circulation time during the attacks but a normal one between attacks.

The circulation time in congestive heart failure may be modified by the presence of an associated disease which itself affects the velocity of the circulation. In particular I have observed a normal circulation time in patients with cardiac failure who also suffered from severe anemia (pernicious anemia, bleeding duodenal ulcer), from hyperthyroidism or from an associated febrile condition. In fact these conditions should always be suspected when a normal circulation time is found in a patient with congestive heart failure. Weiss and Wilkins[161] stressed the diagnostic value of a normal circulation time and a high venous pressure in cases of congestive heart failure due to vitamin B deficiency. I have noted severe heart failure with a normal circulation time in patients with carbon tetrachloride nephrosis and anuria.

Diagnostic Value of the Circulation Time

The chief use for the determination of the circulation time is in confirming the diagnosis of congestive heart failure. By performing both an arm-to-tongue and arm-to-lung test and determining the venous pressure at the same time, the cardiac failure may be attributed to the left or right side of the heart or both. Prolongation of the arm-to-tongue (saccharin, decholin) time with a normal arm-to-lung (ether) time and a normal venous pressure usually denotes pure left-sided failure; prolongation of both and elevation of the venous pressure indicate right-sided heart failure. The simplicity of these tests which can be readily performed both in the office and at the bedside makes them an integral part of the examination of the circulation.

Often the circulation time helps to distinguish cardiac failure from a number of conditions which produce some of the same symptoms.

1. *Asthma.* In cases of bronchial asthma the circulation time is normal or it may be reduced. Asthma due to heart failure is associated with a prolonged circulation time. A normal circulation time excludes cardiac *failure* but not cardiac *disease.*

2. *Dyspnea and Orthopnea.* When dyspnea or orthopnea is due to intrinsic pulmonary disease, the circulation time is normal.[134] But in cases of severe emphysema with diminished arterial oxygen saturation the circulation time may be diminished. In cases of complete unilateral pneumothorax it may be rapid. Dyspnea or orthopnea due to congestive heart failure is accompanied by a long circulation time.

3. *Edema or Ascites.* Edema due to nephritis, nephrosis, postural defects or local venous disturbance, and ascites due to cirrhosis of the liver or neoplasm, are associated with a normal circulation time. In cases of anemia with edema there may be a normal or an abbreviated circulation time.

4. *Hepatic Enlargement and Venous Engorgement.* A determination of the circulation time may aid both in distinguishing hepatic enlargement due to heart failure from that due to intrinsic disease of the liver, and in distinguishing the cervical venous engorgement of heart failure from that due to superior vena caval obstruction.

The circulation time has been found of value in revealing obscure cases of hyperthyroidism. This may be suspected when the circulation time is normal in an obvious case of congestive heart failure without associated severe anemia or avitaminosis. The use of the circulation time measurements in the diagnosis of congenital heart disease is discussed on p. 684.

The circulation time is helpful in estimating the progress and prognosis of a patient with congestive heart failure. As signs and symptoms of congestive heart failure regress, the circulation time diminishes and may revert to normal. It has been noted, however, that the circulation time may increase although distressing dyspnea or orthopnea subsides when right-sided heart failure is added to pure left-sided failure. As a rule, a reduction in the long circulation time indicates improvement.

BLOOD VOLUME

The blood volume refers to the volume of the circulating blood. Direct measurements of the blood volume have been made by exsanguinating animals or decapitated criminals. By this means, the blood volume in humans was found to be one thirteenth of the body weight or between 5 and 6 liters. For clinical purposes, indirect methods must be utilized to determine the circulating blood volume. A known quantity of a foreign substance is introduced into the blood and its concentration in a sample of blood is determined some minutes later, when thorough mixing has occurred. From these two values the blood volume can be calculated. The foreign substance must be nontoxic in the quantity used, must become evenly distributed in the blood, must not diffuse out of the blood to any significant degree within the period of the test, and its concentration in the blood must be readily determinable. As a rule carbon monoxide is introduced by inhalation, [23, 29a] or a colloidal dye[6] such as vital red,[89] Congo red,[145] or Evans blue[60] (T 1824) is introduced intravenously.[59] Recently, radioactive substances have been utilized (p. 144). Phillips et al.[137] have described a method for calculating the blood volume from the fall in specific gravity of blood caused by infusion of a known quantity of isosmotic plasma or albumin solution at the rate of 50 to 100 ml. per minute.

Determination of the Circulating Blood Volume

Evans Blue (T 1824). This blue dye has been found preferable to the red colloidal dyes because its estimation is not impeded by similarity to the inherent color of plasma or by the occurrence of hemolysis. The details of the method using Evans blue are reported by Gibson and Evans,[51] and modifications have been described by others.[61, 59] Instead of an ordinary colorimeter, a spectrophotometer or photoelectric colorimeter[52, 90] is employed so that the color strength is read in absolute terms (optical density). The concentration of the dye is determined from the reading of the colorimeter by a previously prepared curve. This curve is made from colorimetric readings obtained with mixtures of known quantities of dye and serum. The resulting colorimeter readings are charted so as to be convertible into cubic centimeters of plasma. To eliminate plasma color, Morris[123] has recommended adsorption of the blue dye on a column of aluminum hydroxide and magnesium oxide and eluting with hydrochloric acid-ethanol mixture. I have found this a distinct improvement.

Method. The subject's height and weight are taken and his surface area calculated.

About 10 cc. of blood is withdrawn without stasis into a dry centrifuge tube containing oxalate or heparin, and the tube is inverted several times.

Exactly 5 cc. of a 0.5 per cent solution of Evans blue (T 1824) is injected intravenously.

In 10 minutes exactly, 10 cc. of blood is withdrawn from another vein and added to a dry tube containing anticoagulant.

From the first tube enough blood is put into a Wintrobe tube and the hematocrit determined by centrifuging for 1 hour at 3000 R.P.M.

The remainder of the dye-free specimen, as well as the specimen of blood containing dye, is centrifuged.

The dye-free plasma is drawn off and read as a blank in the colorimeter and the plasma containing dye is likewise read in the colorimeter.

From the prepared curve the plasma volume is calculated and the red cell volume and total volume determined from the hematocrit.

For greater accuracy multiple specimens of blood should be taken at intervals of five, ten, fifteen and twenty minutes after injection of the dye and appropriate calculations made from the mixing curve obtained from the concentration values of the dye in these specimens.

Radioactive Substances. Radioactive iron fed to a subject is converted into hemoglobin and this tags the newly formed erythrocytes. After several weeks, a measured amount of blood taken from this subject (donor) is injected into the recipient whose blood volume is to be determined. After about 10 minutes a measured amount of blood withdrawn from the recipient is compared for radioactivity with that of a similar measured sample of blood from the donor. The determinations of radioactivity are made on wet-ashed corpuscles by means of a Geiger counter.[67, 136, 55] This gives an absolute measure of the *circulating* red cells which is independent of the hematocrit. It has been used in conjunction with the dye method for plasma volume to measure the circulating total blood volume.

In a similar manner the red cell volume can be determined by tagging erythrocytes with radioactive phosphorus.[66, 131] The subject's own erythrocytes can be activated with P^{32} in vitro and injected after being washed free of plasma.[140a] Plasma volume has been determined by injecting albumin or plasma containing radioactive iodine.[44]

The Normal Circulating Blood Volume

The normal circulating blood volume as determined by the red dye method is about 70 to 100 cc. per kg. of body weight.[20, 19] Of this, 40 to 55 cc. per kg. represents the plasma volume. The values found by the carbon monoxide method are lower, averaging 60 to 75 cc. per kg. for the total volume.[23] In obese persons the circulating blood volume is lower in relation to the body weight than the figures stated, while in emaciated persons it is higher. The normal blood volume has a more constant value when related to surface area than to body weight.[19] But in persons who have undergone considerable changes in weight due to disease, obesity or accumulation of edema, the most accurate standards of blood volume are obtained when related to height. The total blood volume is 2500 to 4000 cc. per square meter when determined with the red dyes and 2000 to 2900 cc. per square meter when determined by the carbon monoxide method. The blood volume is slightly less in females

than in males. This difference is due chiefly to the greater red cell volume in males.

Recent determinations of the normal blood volume by means of Evans blue and the spectrophotometer probably give more accurate values than those determined by the red dyes. With the blue dye method Gibson and Evans[51] found the total blood volume to range between 65 and 95 cc. per kg. (average 78 cc. per kg.) for males and between 60 and 85 cc. per kg. (avg. 66 cc. per kg.) for females. The red cell volume as calculated by the hematocrit from the dye-plasma volume tends to be too high by 15 to 20 per cent as compared with the more direct and accurate determinations with radioactive iron.[53, 118] This is due to the fact that the hematocrit of venous blood taken from a large (antecubital) vessel exceeds that of capillary blood and therefore of the average body hematocrit.[54] This also accounts for the higher values calculated for erythrocyte volume from the dye-plasma volume and hematocrit as compared to the values for erythrocyte volume obtained by the carbon monoxide method,[78] but Courtice and Gunton found satisfactory agreement between the carbon monoxide and T 1824 dye method.[29a]

Physiologic and Pathologic Variations in Blood Volume

Increased Blood Volume. The circulating blood volume is *increased* with elevation of the environmental temperature, with altitude, during muscular exercise, intense emotion and progressively during the latter half of pregnancy (p. 1018). The blood volume increases temporarily following rapid transfusions and infusions or after the oral administration of large amounts of sodium salts.[56, 108]

The following *pathologic conditions* are also associated with an increase in blood volume which may be due essentially to an increased plasma volume, an increased cell volume or both:

1. Polycythemia vera and secondary polycythemia (chiefly or exclusively red cell volume).
2. Leukemia (white blood cells and plasma).
3. Cirrhosis of the liver (plasma).
4. Splenomegalic anemias (plasma increased, red cells diminished).
5. Hyperthyroidism (red cells and plasma—slight).
6. Cushing's syndrome (chiefly erythrocytes).
7. Congestive heart failure (see below).

Diminished Blood Volume. The circulating blood volume is *reduced* on exposure to cold, after sweating, after prolonged abstinence from fluids, after anesthesia and after standing erect for one-half hour or more. It is also reduced by a low salt diet and by diuretic drugs such as the mercurials, acidifying salts[109] or urea.

The most important *pathologic conditions* associated with a reduction in the circulating blood volume are:

1. Hemorrhage (plasma and cells).
2. Various forms of shock (see Chapter 10).
3. Diseases associated with severe diarrhea (plasma).
4. Diseases associated with persistent vomiting (plasma).
5. Myxedema (red cells and plasma—slight).
6. Chronic glomerulonephritis (red cells reduced, plasma increased).

7. Severe pernicious anemia (red cells greatly reduced, plasma increased slightly).

The Circulating Blood Volume in Congestive Heart Failure

The clinical observation of intense venous engorgement (high venous pressure, distention of superficial veins, hepatic enlargement and pulmonary congestion) suggests the presence of an increased blood volume since there is no corresponding depletion of the arterial system to compensate for the venous engorgement. The absence of arterial depletion is indicated by the maintenance of arterial blood pressure and absence of cold extremities or other phenomena of shock. An increase of blood volume in cases of congestive heart failure is also indicated by the pathologic observation of dilated cardiac chambers and by the intense engorgement of the blood vessels and viscera, including the lungs, liver and gastrointestinal tract.

Actual determinations of the circulating blood volume, while in some disagreement, mostly reveal a definite increase in patients with congestive heart failure.[51, 138, 144, 39, 117] Hamilton and his co-workers[70] demonstrated an augmentation of the intrathoracic blood volume, the volume of blood in both the heart and in the lungs being increased during congestive heart failure, but not in patients with compensated heart disease. Gibson and Evans[51] found the total blood volume definitely increased during congestive heart failure, but especially in patients whose venous pressure exceeded 10 cm. of water and whose circulation time was prolonged. When the venous pressure was above 15 cm. of water, the average increase in the circulating blood volume was roughly parallel to the prolongation in circulation time and the elevation of the venous pressure. With the subsidence of symptoms the blood volume fell, the diminution being greatest in those patients with the greatest clinical improvement. In most patients the blood volume decreased a liter or more and occasionally there was a reduction of 3.5 liters.

Wollheim[167] also found, in extensive studies of the circulating blood volume, that this was increased in most patients with cardiac failure. A study of his cases reveals that the patients with an increased blood volume were suffering from congestive heart failure, termed by Wollheim[167] plus decompensation. Of the patients with a diminished blood volume (40 to 60 cc. per kg.), the so-called group of minus decompensation, many included instances of shock with or without congestive heart failure. Insufficient clinical data are provided in Wollheim's publication to permit an interpretation of his cases and findings.

EXTRACELLULAR AND INTRACELLULAR FLUID VOLUME

The general belief has been that total body water forms about 70 per cent of the body weight, 50 per cent consisting of intracellular fluid and 20 per cent of extracellular fluid. More recent determinations by the dilution of deuterium oxide ("heavy water") and of antipyrine have shown that total body water averages about 55 per cent in males and somewhat less in females.[10a] Measurement of the extracellular fluid with the aid of inulin has disclosed that the former amounts to 15 per cent of the body weight, instead of 20 per cent or more as was previously maintained.[104a] The extracellular fluid is further subdivided into plasma volume forming about 5 per cent and the extravascular interstitial fluid forming about 10 per cent of body weight. By subtraction the intracellular fluid accounts for 40 per cent of the body weight.

The extracellular volume has been measured by injecting known amounts of substances, which are mixed uniformly throughout the extracellular fluid. Sodium thiocyanate[30, 103, 151] has been used most frequently, but also mannitol,[36] radioactive sodium,[88, 121] bromide[41a] and other substances. Gregersen and Stewart[62] described a method for the simultaneous determination of the plasma volume and extracellular volume by means of T 1824 and sodium thiocyanate. None of the substances used for determining the extracellular fluid volume is satisfactory. Studies of the extracellular space with these substances give values which are apparently too high, for when they are subtracted from the values for total body water the remainders, denoting intracellular water, are too small to be credible.[10a] It is probable that these substances, including sodium, are not confined to the extracellular space but also enter the cells themselves to a much greater extent than was hitherto believed. This may not apply to inulin, which may therefore provide a more accurate means of measuring extracellular fluid.

In cases of congestive heart failure, the interstitial fluid and total extracellular volume increase as does the blood volume. It is probable that shifts of water and electrolytes occur in congestive heart failure and that the intracellular fluid may also be augmented in the course of heart failure. By determining the total body water and intracellular water as indicated above, and by measuring the in vivo dilution of injected radioactive Na^{24} and K^{42} it is possible to estimate the intracellular concentration of these important kations. There is evidence in the dog that the concentration of intracellular sodium is much higher than was formerly believed.[104b] Newer methods ought to reveal more directly whether in cases of heart failure shifts of sodium, potassium and water occur between the extracellular and intracellular compartments as is suggested by indirect balance studies.

VENOUS PRESSURE

Clinical measurement of the venous pressure is limited to the systemic (caval) venous branches. However, an elevation of the pulmonic venous pressure can often be surmised when there are physical signs of congestion or edema of the lungs or roentgenologic evidences of pulmonary congestion in patients with cardiac disease.

It is clinically desirable to determine the pressure in the systemic veins near their entrance into the right atrium. As a rule the pressure in these great veins is not determined directly; instead, some more accessible vein nearby such as the external jugular vein or an antecubital vein is used. To eliminate the factor of hydrostatic pressure, the patient is examined in the supine position with the vein under consideration placed at the level of the right auricle. This may not be a precise correction for there is some evidence that the zero reference point is not at the level of the base of the atria but some distance below.[26] The mean right atrial pressure in normal subjects is -2 to $+2$ mm. Hg relative to atmospheric pressure.[13]

The measurement of the venous pressure can be made by clinical inspection, by indirect methods or by direct cannulation of a vein.

Estimation of the Venous Pressure by Clinical Inspection. It was suggested by Gaertner[49] that when an extremity is elevated its veins represent a manometric column in communication with the right atrium. The arm is elevated until a visible vein collapses. At this point, the venous pressure is just balanced by

the hydrostatic pressure in the vein. The height of the collapsed vein above the level of the atrium represents the venous pressure. This method is useful only when the venous pressure is higher than normal. The veins on the undersurface of the tongue have also been used to determine an elevation in venous pressure.[113] Normally these are collapsed when the patient is sitting. They become notably engorged when the venous pressure exceeds 20 cm. of water.

The use of the external jugular vein for estimating venous pressure has been emphasized by Lewis.[105] Normally when the subject sits or stands erect, this vein fills to the root of the neck, the height of filling increasing as the subject becomes more horizontal. When the subject is recumbent the venous filling reaches a point which is on a horizontal level with the lower border of the manubrium sterni or the zero point of reference. If the venous pressure is increased above normal, the level of venous filling is correspondingly elevated. Thus with congestive heart failure, the jugular vein may be visibly filled for 2 or more cm. above the level of the clavicle even when the patient is upright. As the head and shoulders are lowered, the height of venous filling increases and may reach to the angle of the jaw. If the height of filling is not distinct, gentle pressure over the lower end of the vein for a few minutes will accentuate the filling; the pressure is then released and the vein observed again.

Sometimes it is simpler to observe the jugular venous pulse. The highest point to which this rises gives the level of venous filling and consequently measures the venous pressure. When the superficial veins of an extremity are clearly visible, e. g., on the dorsum of the hand, the venous pressure may be roughly estimated as the height to which the extremity must be elevated above the atrium in order to cause the vein to collapse.

Indirect Method of Determining Venous Pressure. The indirect method[40, 99, 10] involves the determination of the external pressure necessary to cause a superficial vein to collapse, this pressure being equal to the venous pressure. A transparent, sometimes illuminated capsule with grooved edges is sealed with colloidin over the vein to be studied. Air is introduced into the capsule by an air pump or bulb until the vein collapses, while at the same time a connecting water manometer is observed for the exact pressure at which venous collapse is effected. The system must be airtight. The venous pressure can be determined in any position of the patient and the hydrostatic pressure may then be eliminated by subtracting the vertical height from the vein to the level of the manubrium sterni. This method is too inaccurate for general clinical use.

Direct Methods of Measuring Venous Pressure. Stephen Hales[68] first made direct measurements of the venous blood pressure by noting the height to which the blood rose in tubes inserted into the jugular vein of animals. Present direct methods include that of Moritz and Tabora[122] or some modification such as that of Taylor, Thomas and Schleiter.[154] My experience is concerned chiefly with the latter method which I have found eminently satisfactory for practical bedside use. The modification proposed by Griffith et al.[63] has also been extensively used. An aneroid type of manometer ("phlebomanometer") was devised by Burch and Winsor.[21]

Method of Moritz and Tabora.[122] Insert into the median basilic vein a needle connected by adapter and tubing to a calibrated buret containing saline. The saline and the apparatus must be sterile. The saline is allowed to enter the vein until the inflow ceases. At this point the level of the saline above that of the right atrium represents the venous pressure. Moritz and Tabora[122] found

the normal venous pressure to vary between 1 and 9 cm. water and most frequently between 4 and 8 cm.

Method of Taylor, Thomas and Schleiter.[154] A sterile L-shaped calibrated glass tube, 30 cm. in length and of 4 mm. bore, is used, the short limb being ground to fit an 18 gauge intravenous needle. The tube or manometer is moistened with 5 per cent sodium citrate solution to inhibit coagulation. The patient is supine with his upper extremity relaxed and abducted from the body at an angle of about 60°. This is to avoid compression or torsion of the axillary or subclavian vein when the arm is close to the body. The subject should rest at least 15 minutes before the procedure is begun. A pillow or towels are placed under the arm to be used so that the antecubital vein is 5 cm. below the horizontal plane of the anterior surface of the sternum at its fourth costochondral junction. This represents approximately the level of the opening of the venae cavae into the right atrium. The patient is instructed to relax and breathe naturally to avoid muscle tension or abnormal changes in intrathoracic pressure.

A sphygmomanometer cuff applied to the arm is inflated to 40 mm. Hg, or a tourniquet may be used. The needle is inserted cleanly into a large antecubital vein so as to obtain a free flow of blood and the cuff is promptly deflated. In the lower extremity the femoral vein may be used, the puncture being made upward and inward 2.5 cm. distal to the inguinal ligament and just medial to the pulsating femoral artery. The height of the column of blood, when it comes to rest in the tube, represents the venous pressure. Consecutive readings should be made until they are constant. The presence of a free communication with the blood stream is indicated by small excursions of the blood in the tube during respiration, by a rise of the blood level in the tube when the cuff is inflated again and by a return to the previous level when deflated.

It is apparent that because of gravity, the venous pressure is considerably higher, especially in the lower extremity, when the subject is standing than when he is recumbent. To neutralize this hydrostatic effect, the vein used for measuring pressure is kept at that level in the right atrium at which the pressure is zero. This is known as the zero or reference level. I have generally used a level of 5 cm. below the horizontal level of a plane through the fourth costochondral junction, depending on the approximate thickness of the chest wall. Lyons et al.[110] have used a level 10 cm. above the level of the skin of the subject's back when in the recumbent position, and Evans[38] and Hussey,[81] the midaxillary line. Winsor and Burch[166] have used a "phlebostatic level" which for the supine position is a horizontal plane half the distance from the base of the xiphoid to the table and in the upright position through the fourth intercostal space. These reference levels are equally valuable if consistency is maintained in all readings.

Aneroid "Phlebomanometer" of Burch and Winsor.[21] This is an aneroid type of manometer calibrated in millimeters of water. The pressure in the vein is balanced by the pressure in the manometric system which is attained by mechanical compression of a pressure bulb. A glass adapter of 1 mm. bore, containing citrate solution, connects the manometer to a 23 gauge needle which is inserted into an appropriate vein. When the column of citrate solution, balancing the venous blood pressure, comes to rest the pressure is read from the scale of the manometer. The aneroid manometer should be checked from time to time against a direct water manometer.

Normal and Pathologic Venous Pressures. The normal venous pressure in an antecubital vein at the level of the right atrium is 4 to 8 cm. water as determined by the direct method. Greater variations have been noted by Moritz and Tabora[122] (1 to 9 cm.), by Hussey[81] (4 to 12 cm.) by Holbrook[77] (1 to 10 cm.) and by Lyons et al.[110] and Winsor and Burch[166] (5 to 14 cm.). In my experience with the method of Taylor and his co-workers,[154] the normal venous pressure rarely exceeds 10 cm. or falls as low as 3 cm. water. The venous pressure is the same in the upper and lower extremities when the veins are at the reference level of the heart.[63, 42, 166] The venous pressure in children is essentially identical with that in adults.[101, 86]

The venous pressure is increased by exercise, but usually returns to normal or lower within a minute after its cessation.[152] With heart failure, the elevation is much greater and it returns slowly to its previous level. The venous pressure falls about 0.5 cm. with quiet inspiration and rises to the same degree with normal expiration. Cough and the Valsalva test increase the venous pressure. The Müller experiment diminishes the venous pressure. An infusion of 500 to 1500 cc. of normal saline or of 5 per cent glucose solution may cause a significant increase in venous pressure only if more than 20 cc. per minute is administered.[3, 32]

The venous pressure is elevated in the following *pathologic conditions:*

1. *Right-sided heart failure.* Usually the venous pressure is between 10 and 20 cm., but it may rise as high as 30 cm. or more. Occasionally the venous pressure is only slightly elevated or even normal despite the presence of distinct hepatic enlargement and subcutaneous edema. In such cases, compression of the abdomen causes an elevation of venous pressure of 2 cm. of water or more.[142, 133, 74] At the same time the jugular veins may become visibly engorged. The more advanced the heart failure, the higher the venous pressure and the greater the elevation following abdominal compression. In normal subjects abdominal pressure causes no change or more often a slight fall in venous pressure in the upper extremity (p. 75).[75]

In pure left-sided failure the systemic venous pressure is normal. The venous pressure is often below 10 cm. in patients with cardiac dyspnea and orthopnea and a prolonged circulation time. Presumably the pulmonary venous pressure is elevated but is not measurable. Indirect evidences of elevated pulmonary venous pressure and venous engorgement are the prolonged circulation time and pronounced reduction in vital capacity. In peripheral circulatory failure and in cardiac shock with strikingly diminished output, the venous pressure is reduced to 3 cm. or less. In cases of acute coronary occlusion there is often a combination of shock and congestive heart failure, the venous pressure depending on which factor predominates. Sometimes in cases of shock, the veins of the extremities are collapsed but the jugular veins are engorged and their pressure high.

2. Constrictive pericarditis. The venous pressure is extremely high, usually above 20 cm. Even slight abdominal compression causes a sharp rise so that the pressure exceeds 30 cm. and the blood flows over the top of the tube.

3. Pericardial effusions with cardiac tamponade.

4. Thrombosis of the venae cavae.

5. Mediastinal tumors, aortic aneurysm, etc.[81]

6. Obstructive emphysema and bronchial asthma, when associated with an increased intrapleural pressure and consequently with increased resistance to

venous inflow.[97] The majority of patients with pulmonary emphysema have a normal venous pressure.[159]

7. Local venous obstruction due to compression or thrombosis.

Clinical Application of Determination of Venous Pressure. The chief value of determining the venous pressure is in the diagnosis and differential diagnosis of right-sided congestive heart failure. This diagnosis is usually indicated, especially in a patient with known cardiac disease, if the venous pressure is elevated or if it rises more than 1 cm. after abdominal compression. Other causes of elevated antecubital venous pressure can usually be excluded by roentgenologic examination of the chest with special reference to the lungs, aorta and mediastinum. Simultaneous determinations of the venous pressure and circulation time distinguish pure left heart failure, pure right-sided heart failure and combined heart failure.[84]

In right-sided heart failure the venous pressure is universally elevated. Universal elevation of the venous pressure, i.e., in the upper and lower halves of the body, is also observed in cases of constrictive pericarditis and pericardial effusion with tamponade. Obstruction to the superior vena cava by aortic aneurysm, mediastinal or pulmonary masses, or thrombosis produces an increased venous pressure only in the upper extremities.[83] Clinical inspection will also show venous engorgement limited to the upper part of the body. Furthermore there is usually a visible collateral circulation in the anterior chest wall with a flow of blood from above downward. Neither right-sided heart failure nor constrictive pericarditis produces sufficient venous obstruction to lead to the development of a visible collateral circulation. I have seen a case of thrombosis of the superior and inferior venae cavae, of unexplained etiology, which caused a universal elevation of venous pressure, but this generalized elevation of venous pressure could be distinguished from that due to heart failure because there was a visible collateral circulation in the chest wall.

Obstruction to the venous return through the inferior vena cava produces an elevated venous pressure only in the lower extremities. This may be observed with pregnancy, abdominal tumors with and without ascites, hypernephroma and other renal tumors invading the inferior vena cava, hepatic tumors and thrombosis of the inferior vena cava.[82]

A local venous obstruction, e.g., in a subclavian vein, will cause an elevation of venous pressure only in peripheral veins of the affected arm. Obstruction due to an aneurysm of the aorta usually causes greater elevation in the left than in the right arm.

In cases of constrictive pericarditis the venous pressure is extremely high and the elevation after abdominal compression is usually greater than in cases of right-sided heart failure secondary to left-sided failure. Furthermore, the circulation time may be normal in contrast with the prolonged circulation time in the latter cases. In cases of cardiac tamponade the high venous pressure is associated with a small pulse, a low blood pressure and the clinical picture of shock.

Comparative measurements of the venous pressure in the upper and lower extremities are of diagnostic value in distinguishing heart failure from superior vena caval obstruction. They also differentiate hepatic enlargement, edema and ascites due to right-heart failure from similar findings due to other conditions.[42] When enlargement of the liver is due to neoplasm or cirrhosis or when peripheral edema is due to nephritis, avitaminosis, or local orthopedic or venous

abnormalities in the legs without associated right-sided heart failure, the venous pressure in the arm veins is normal. The venous pressure in the lower extremities may or may not be elevated.

Repeated determinations of the venous pressure are valuable in the prognosis and treatment of right-sided heart failure. Improvement is frequently denoted by a progressive diminution of the venous pressure. Conversely, a persistently high venous pressure despite rest in bed and the administration of digitalis and mercurial diuretics indicates a poor prognosis. In cases of constrictive pericarditis these measures do not significantly reduce the venous pressure but effective surgical release of the heart is followed by a return of the venous pressure to normal. An extremely high venous pressure due to congestive heart failure is sometimes interpreted as an indication for venesection, but other clinical features should also be considered.

THE VITAL CAPACITY

The popularity of determining the vital capacity has undergone wide fluctuations since Hutchinson[85] in 1846 made the first scientific study of this test in 3000 subjects. Interest in this question was stimulated in this country by the work of Peabody and his co-workers.[135] But in recent years the determination of the vital capacity has been relegated to a secondary place as a test of circulatory function due to the greater value of such tests as circulation time and venous pressure, the wide range of normal figures for vital capacity and the variety of physiologic and pathologic factors which may alter it. (For a survey and criticism of the vital capacity test, see Fleisch.[46])

On the other hand, the test is a simple one, is easy to perform and requires no apparatus but a spirometer. In any given patient with heart disease, successive measurements have a comparative value in following the progress of the disease. Sometimes a significant reduction in vital capacity precedes such physical signs as râles at the bases of the lungs in left-sided heart failure. Successive determinations of the vital capacity may be utilized as an objective record of the effect of therapy. The vital capacity test may distinguish the dyspnea due to congestive heart failure from that associated with the effort syndrome, for the vital capacity is normal in cases of the latter condition.[2]

Method of Determining the Vital Capacity. A spirometer is used to measure the amount of air exhaled. The subject, who maintains the same position throughout the test (usually sitting or erect), is instructed to inspire as deeply as possible from the outside air and then to expire as deeply as possible into the tube connected with the spirometer. Three attempts are made and the highest value is recorded as the vital capacity.

The Vital Capacity in Health. The normal vital capacity varies considerably according to the height, weight, general build and sex. Hutchinson[85] utilized standards based on height. Recent tables of vital capacity standards according to height are given by Cripps, Greenwood and Newbold.[31] Standards based on chest measurements and trunk height are also available. Height standards are most reliable in persons who have undergone sharp changes in weight or who are strikingly obese or edematous. However, ordinarily the most reliable standard of vital capacity is that referred to the surface area. The surface area is determined by measurements of the subject's height and weight according to the tables of Du Bois and Du Bois.

The normal standards of vital capacity formulated by West[162] and by

Myers[124] in terms of surface area have attained wide usage. According to West[162] the average vital capacity is 2500 cc. per square meter in men and 2000 cc. per square meter in women. In muscular persons the vital capacity averages 10 to 15 per cent higher. In terms of height the average vital capacity is 25 $\times$ height in cm. for men and 20 $\times$ height in cm. for women. Standards for children have been published by Edwards and Wilson.[34] They found an average vital capacity of 15.5 cc. for each centimeter in height. For purposes of interpretation, the vital capacity as determined is expressed as a percentage of the expected normal vital capacity for the subject as calculated from tables for his sex, height and weight.

The following factors, as well as body measurement, influence the vital capacity:

1. Age. Children have a lower vital capacity than adults. Between twenty and fifty years, age has no significant effect. The vital capacity diminishes after the age of fifty and drops more rapidly after the age of sixty.
2. Sex. In adult life, the vital capacity averages 20 per cent lower in women than in men.
3. Muscular development. Athletes may have a vital capacity which is 10 to 100 per cent greater than the theoretical normal for their height or surface area. Persons engaged in occupations requiring muscular effort have a larger vital capacity than those engaged in sedentary occupations.
4. Posture. According to Christie and Beams[25] the vital capacity averages 5.5 per cent more when the subject is standing than when recumbent.
5. Atmospheric conditions. In high altitudes there is a considerable diminution of the vital capacity. According to Apperly,[4] corrections for temperature and atmospheric pressure must be made in the values for vital capacity as obtained with the spirometer. Otherwise there may be a significant apparent lowering of the vital capacity in the winter as compared with the summer.

Pathologic Conditions Altering the Vital Capacity. The vital capacity is determined by the force of contraction of the thoracic, abdominal and diaphragmatic muscles, the flexibility of the thoracic cage, the elasticity of the lungs and the available space in the thoracic cavity and the alveoli of the lungs. Thus pathologic conditions which impair any of these factors may reduce the vital capacity. The following diseases are most commonly associated with a reduction in vital capacity.

1. Heart disease complicated by cardiac failure.
2. Pulmonary and pleural diseases, including pulmonary tuberculosis, pneumothorax, emphysema, pneumonia, pulmonary abscess or neoplasms, pleural effusions.[80]
3. Diseases of the thoracic wall, including severe muscular weakness or paralysis, calcifications of the cartilages, ankylosis of the thoracic joints.
4. Abdominal diseases which interfere with the enlargement of the thoracic cavity during respiration, e.g., abdominal tumors, ascites, enlargement of the liver or spleen and sometimes pregnancy.
5. Hyperthyroidism.

The Vital Capacity in Heart Failure. The vital capacity is normal in compensated heart disease. A diminution in vital capacity may be the earliest objective sign of congestive heart failure. Like cardiac dyspnea, the diminished vital capacity is due to the pulmonary congestion of left-sided heart failure and the consequent rigidity of the lungs and diminution in alveolar space. In patients

with right-sided heart failure the vital capacity is also reduced, either because of the associated left-sided failure or primary pulmonary disease.

The reduction in vital capacity roughly parallels the intensity of cardiac dyspnea and the clinical severity of congestive heart failure. McClure and Peabody[114] classified patients with heart failure according to the percentage of reduction in vital capacity. Patients with a vital capacity between 70 and 90 per cent of normal became dyspneic only with moderate exertion but were capable of some work. Those with vital capacities between 40 and 70 per cent of normal were incapable of work because of dyspnea on slight exertion. When the vital capacity was less than 40 per cent of normal, the patients were usually dyspneic at rest and confined to bed.

A reduction in vital capacity may be considered to indicate the presence of cardiac failure only if the other causative pathological conditions mentioned above are excluded. Even then a low vital capacity is of only limited significance unless comparative measurements are available over a period of time.[139, 5] The vital capacity test is less valuable than the circulation time as an index of left-sided heart failure because the circulation time is not modified by the numerous diseases which may reduce the vital capacity, and because it is independent of height, weight or surface area of the patient. As a rule, the vital capacity is diminished in cardiac patients with prolonged circulation time, i.e., with left-sided heart failure. I have found repeated determinations of the vital capacity of value in cardiac patients requiring intravenous infusions or multiple transfusions. A pronounced reduction in the vital capacity is a danger signal, warning of impending pulmonary edema.

TESTS OF MYOCARDIAL RESERVE

The various circulatory tests considered thus far are designed to reveal the presence or absence of cardiac failure. In most cases of cardiac *disease* without failure, these tests may all yield normal results. This merely indicates that the circulatory compensations for the disease are adequate to maintain a normal circulation when the patient is at rest or performing his ordinary activities. Additional tests have been designed to determine the adequacy of the circulatory response when some special strain is placed on the circulatory system. These are really attempts to test the myocardial reserve (p. 3).

Tests of myocardial reserve[104, 155a] usually note the effect on the pulse rate, the blood pressure or the respiratory rate after the patient performs some procedure which strains the circulation. Most often this strain is effected by some form of physical exercise, but breath-holding, the Valsalva procedure, immersion in warm bath, and others have also been employed. In addition to observing the effect on the pulse, blood pressure or respiration, one may also study the effect on the electrocardiogram, the size of the heart or the consumption of oxygen.[132, 24a]

A commonly used, simple test consists of recording the pulse rate before and after the subject changes from the sitting to the standing position, after 10 knee-bendings or after hopping 50 times on one foot. If the original pulse rate is 80 per minute, the increase in rate should not exceed 10 on standing, 20 after knee-bending or 30 after the hopping. In each of the tests the pulse rate should return to the original level within two minutes. As a result of the test the blood pressure should not rise more than 10 mm. Hg and should return

to the initial level within two minutes. The respiratory rate should not increase more than 6 per minute. Messinger[119] has stressed the value of observing the ratio of the pulse rate to the respiratory rate. In normal subjects, this ratio increases with exercise; in patients with cardiac disease it does not increase. Thus the ratio after an exercise test in normal persons was found to be 5.5 but in cardiac patients it was less than 4.5.

Efforts have been made to standardize these exercise tests so that a fixed amount of exercise is performed in a given time, the amount depending on the age, sex and weight of the subjects. Such a standardized exercise tolerance test involving a variable number of ascents of two steps, each 9 inches high, in a period of one and a half minutes was described by Master and Oppenheimer.[112] The number of climbs for each subject is determined from tables. In normal persons, the pulse rate does not rise more than 10 beats per second and the blood pressure not more than 10 mm. Hg. Both return to the initial level in two minutes.

The clinical history is often a better guide to the patient's response to exercise than any of the utilized objective tests. The amount of activity required to produce dyspnea and any change in the ability to perform usual activities without dyspnea are often revealing as to the maintenance or reduction of normal cardiac function. Due care is required in the interpretation of dyspnea and its differentiation from sighing respiration. The possible role of pulmonary disease, obstructive diseases of the respiratory tract, recent excessive weight gain and obesity, requires careful study.

A variety of other tests of myocardial reserve have been described. One of the simplest is the breath-holding test. The normal person can hold his breath for 30 seconds or longer. Subjects with limited cardiac reserve cannot usually do this for more than 20 seconds. The same test may be performed immediately after some exertion such as 10 knee-bendings. After such exercise the patient with diminished cardiac reserve cannot usually hold his breath for more than 12 seconds. A modification of this test consists in observation of changes in the pulse and blood pressure while the subject is blowing through a tube against a fixed pressure. The Schellong test requires a subject to stand for ten to twenty minutes during which time continuous measurements of his blood pressure are recorded. Poor circulatory function is denoted by a fall of the systolic blood pressure of 20 mm. Hg or more. The subject may collapse if the drop in pressure is excessive, especially if he suffers from postural hypotension.

During the Valsalva test, the heart in normal persons becomes smaller, as observed by fluoroscopy. In patients with poor myocardial reserve it may dilate. Electrocardiographic studies following exercise have also been utilized to demonstrate poor myocardial or coronary circulatory reserve (p. 381). Similar electrocardiographic changes are produced by breathing procedures associated with anoxemia (Chapter 18).

Nylin[132] utilized the determination of the oxygen debt after exercise as the basis of a test of circulatory function. After a standard exercise which consists of stair-climbing, Nylin[132] observed that the increase in oxygen consumption (i.e., the oxygen debt) is much greater in subjects with diseased hearts than in normal persons. A diminished capacity for increasing the cardiac output during exercise is the basis of a cardiac function test utilized by Neukirch.[128]

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9

THE TREATMENT OF CONGESTIVE HEART FAILURE

Treatment of the Underlying Causes of Heart Failure. In order to treat congestive heart failure most effectively it is desirable to determine the etiologic factors responsible for its development. In many cases, e.g., those due to hypertension or coronary artery disease, no specific treatment can be applied to the etiologic factor. But when heart failure is secondary to a recent coronary occlusion or to an activation of rheumatic fever, a longer period of rest in bed may be necessitated by the causative disease than would be required for the management of the heart failure itself. In still other cases of congestive heart failure, the major element in treatment is the cure or alleviation of the underlying cause. Thus thyroidectomy or antithyroid medication in cases of heart failure due to Graves' disease, decortication of the heart in those due to constrictive pericarditis, and closure of the fistula in those due to an arteriovenous aneurysm are often life-saving measures without which treatment of heart failure per se is futile. Similarly specific medical treatment of vitamin B deficiency, hypothyroidism, anemia or diphtheria toxemia may be curative in cases of heart failure associated with beriberi heart disease, myxedema heart, chronic or acute hemorrhage or diphtheria, respectively.

When cardiac failure appears early during pregnancy, a therapeutic abortion may be necessary to alleviate the symptoms. When cardiac failure is precipitated suddenly by extreme tachycardia such as may accompany a paroxysm of auricular fibrillation, treatment consists of prompt slowing of the heart by digitalis, strophanthin or quinidine. Mild antiluetic therapy directed against the primary cause of failure associated with syphilitic heart disease gives less striking results than in the conditions mentioned above, but it may prolong life.

Preventive Measures. The prevention of cardiac failure in patients with known heart disease is pertinent. Respiratory infections should be avoided, especially in patients with rheumatic heart disease. Limitation of emotional strain and physical exertion is particularly important in patients with hypertensive or arteriosclerotic heart disease. Chronic cough should be controlled by rest, codeine, etc., as the associated strain may precipitate cardiac failure. Lesions associated with recurrent bleeding and anemia, e.g., peptic ulcer or bleeding hemorrhoids, should be cured medically or surgically, especially in patients who already suffer from an insufficient coronary blood supply. The

rapid or excessive intravenous administration of fluids may induce congestive heart failure and should be avoided. The adequate specific treatment of syphilis in patients with early cardiovascular syphilis will prevent or postpone the development of heart failure. Similarly control of hyperthyroidism should be effected before cardiac failure develops. Dietary control of obesity, particularly in middle-aged or elderly cardiac patients, may diminish the probability of heart failure.

Prophylactic periods of bed rest are desirable for patients who have previously suffered attacks of failure. Careful maintenance of digitalization, low sodium intake and other prescribed medication are often essential to avoid recurrence of heart failure after the initial attack is controlled. Avoidance of prolonged or exaggerated bed rest and the use of anticoagulants in cardiac patients requiring surgical procedures may diminish the probability of thromboembolic complications and their precipitation of heart falure.

GENERAL THERAPEUTIC MEASURES

Principles of Treatment. In addition to the elimination or control of the precipitating or contributory factors, treatment consists essentially of the following:

1. *Improvement in cardiac efficiency.* This is effected by (a) limitation of physical activity which reduces the load on the heart and (b) digitalis administration which improves cardiac function, probably by direct action on the heart.
2. *Control of sodium-water retention.* This involves a sharp limitation of sodium intake and the use of diuretics, especially mercurial diuretics, which promote the excretion of sodium and water through the kidneys.

These and other secondary therapeutic measures will be discussed individually in the following pages. However, in execution, most of these therapeutic measures are utilized simultaneously. To obtain maximal effects as soon as possible Gold, Kwit, et al.[74] have recommended a five-pronged program including (a) rest in bed or chair, (b) extreme sodium restriction, (c) daily mercurial diuretics, (d) single dose rapid digitalization and (e) daily weighing as a guide to the removal of extracellular fluid (edema). The program is continued until all gross signs of edema disappear and the body weight reaches a minimal and basic level. Attractive as their routinized program appears, great caution and judgment are essential in its application to individual patients. There is danger in the simplicity of dogmatic therapeutic instructions. In particular, digitalis dosage and the frequency with which mercurial diuretics are administered require considerable elasticity.

It is equally important to maintain therapeutic control after the manifestations of congestive heart failure have been abolished. Activity is limited, but liberalized according to tolerance. Digitalization is maintained. Sodium restriction and the administration of mercurials are continued according to the patient's weight and clinical symptoms. The optimum regime should be maintained as the diabetic's regime is maintained. It is as faulty to discontinue treatment until heart failure recurs, as to restrict diet and administer insulin to the diabetic only when he develops diabetic acidosis. However, occasionally when heart failure is precipitated by an acute infection or the sudden development of severe anemia, compensation is readily established by control of infection or anemia, and may be maintained without continuing digitalis, diuretics or a strict low sodium diet.

Rest. *The Rationale of Rest.* Rest is designed to alleviate heart failure by

diminishing the work of the heart. Heart failure denotes an inability to maintain an output adequate for the needs of the body. Those needs can be minimized by eliminating physical exertion. Hickam and Cargill[92] showed that the patient in heart failure is unable to meet the stress of exercise with an increase in cardiac output, as the normal individual does. Merrill and Cargill[127] found that the renal blood flow in patients with moderate heart failure may be normal with the patient at rest but inadequate with exercise. And Landis et al.[105] observed in experimental heart failure that the venous pressures which were normal with the animal at rest became elevated during exercise. These abnormalities of renal blood flow and of venous pressure induced by activity have been related to the basic disturbances in heart failure (salt-water retention and edema). Activity promotes the venous return and produces pulmonary congestion and dyspnea when the left side of the heart is incompetent. The purpose of bed rest is to avoid these circulatory handicaps imposed by activity.

Rest reduces the work of the heart also by diminishing the blood pressure, thus permitting the heart to contract against a lower resistance. By eliminating dyspnea, rest decreases the work of the respiratory muscles, the oxygen utilization and the work of the heart. By slowing the cardiac rate, it prolongs the diastolic period of recovery and results in improved efficiency of cardiac contraction. The final proof of the value of rest is the rapid alleviation of dyspnea and other symptoms which the patient often discovers for himself. Often, especially when the symptoms of failure are relatively mild and of brief duration, rest alone effects a cure. This was strikingly indicated by Fothergill[59] in 1872.

In recent years attention has been directed repeatedly to the dangers of bed rest.[82, 44, 107] These admonitions should not be misinterpreted. The physician must distinguish between essential bed rest and unnecessarily prolonged bed rest, between the judicious use and the excessive abuse of rest. A distinction should be drawn also between rest and recumbency. For patients with congestive heart failure may obtain the desired rest, with more comfort, propped up in a large chair or bed than when at complete rest in the horizontal position.

The greatest danger of bed rest in patients with heart failure is the invitation to phlebothrombosis and pulmonary embolism. Deep breathing and leg exercises, changes in position and the use of anticoagulants are measures designed to overcome these dangers (p. 882). The hazard of bronchopulmonary infections, always lurking in patients with bronchial or pulmonary stasis due to congestive heart failure, is enhanced by inactivity in bed, especially in the obese, the indolent and the elderly. The restricted judicious use of sedatives and narcotics will minimize the danger of complete immobility of the patient. Exaggerated straining at stool in using a bedpan often enhances the danger of fatal pulmonary embolism.

Elderly patients often become completely bedridden with prolonged bed rest. Osteoporosis, bone atrophy and muscle wasting become intensified. Urinary retention may be precipitated in patients with prostatism. Constipation, cathartic habituation, back strain, bed sores and psychoneurosis are among the other hazards attributed to complete and prolonged bed rest.

Duration of the Rest Period in Bed. Rest may involve a complete stay in bed for a continuous period, confinement during occasional days of the week or hours of the day or various modifications of these, or it may merely consist of a limitation of activity at work or at home. These are discussed below.

According to its severity, heart failure may require the patient to remain in

bed for periods of one to four weeks or longer. Usually in uncomplicated cases of moderate severity, proper treatment combined with such a period of minimal activity suffices to enable the heart to build up a reserve so that symptoms will not readily reappear when normal or moderately limited activity is gradually resumed. On the other hand, in very severe cases, or in patients with a delayed therapeutic response, bed rest may have to be prolonged. The advantages of prolonged bed rest (twelve to seventy-two weeks) as compared with rest for a few weeks were reported by Davis[35] in a comparative study of patients with congestive heart failure. Davis[35] emphasized that bed rest should be continued for a variable number of weeks after the disappearance of evidences of failure in order that the heart may reach an optimum capacity for work.

The whole question of duration of bed rest still requires study. Fixed periods cannot be prescribed for all cases of heart failure since each presents an individual problem. Certainly the very long periods mentioned above are not advisable for many patients with symptoms of moderate severity which respond rapidly to simple measures. When patients have only mild symptoms, such as exertional dyspnea, and when economic restrictions are placed on the rest period, a period of four to seven days in bed may suffice to begin treatment. The response of symptoms to rest and resumption of activity will aid in determining whether longer periods of rest are necessary.

The above-mentioned periods of bed rest may be prolonged not only by a poor therapeutic response but by associated diseases which precipitated failure or by complications of heart failure. Patients with acute coronary occlusion and failure may have to be kept in bed for four to six weeks and often for several months. The patients with active rheumatic fever should remain in bed as long as there are symptoms or signs of rheumatic activity. It must be emphasized that complete bed rest is not terminated merely because the patient has already spent eight, twelve or even twenty weeks in bed. In the final analysis the clinical course of the patient and not an arbitrary time limit is the determining factor.

The resumption of some degree of exertion, as soon as this can be effected without danger, serves to improve muscular tone which aids the venous return to the heart and increases general physical fitness. Rest should not be prescribed at all for patients whose dyspnea is associated with neurocirculatory asthenia or anxiety neurosis. Neither is rest indicated merely because of the presence of cardiac disease if this disease is well compensated. On the contrary, controlled physical training is desirable in these conditions in order to enable the patient to carry on normal activities.

Complete Bed Rest. Sometimes rest in bed fails to bring about a satisfactory symptomatic improvement until it is rigidly enforced and activity is absolutely proscribed. Bathroom privileges, trips to the telephone, getting out for meals and occasional excursions out of the bedroom may completely nullify the therapeutic effect of rest in bed. When heart failure is associated with coronary thrombosis, active rheumatic fever or other febrile diseases, or when it fails to respond to partial limitation of activity, complete bed rest must be enforced.

Complete bed rest does not imply that the patient must lie flat in bed. Usually he is most comfortable if his head and shoulders are propped up by two or more pillows. Special beds which permit elevation or depression of the upper or lower ends are ideal for obtaining the proper elevation of the head and chest. When orthopnea is intense, the position of the bed should be fixed so as to place the

patient in a sitting position. If the bed is not adjustable, the patient may sit at the side of the bed with his feet hanging onto a chair and his back and head supported by pillows. Adequate rest with maximum comfort is often best attained in a large cushioned chair. Patients with severe congestive heart failure usually have a remarkable capacity for finding the position best suited for their circulatory status and the physician should help them attain and maintain that position with comfort and not arbitrarily modify it.

The enforced use of the bedpan is often a distortion of the purpose of bed rest. Straining at stool involves the Valsalva procedure and the concomitant risk of pulmonary embolism. It is obvious that many patients will profit more from permission to use the commode at the bedside or even from one daily trip to the bathroom if necessary than they risk from these slight activities. Elderly patients with prostatic enlargement likewise benefit more from commode or lavatory privileges than from extreme restriction to bed. Similarly leg and breathing exercises and frequent changes of position in bed, by minimizing the risk of phlebothrombosis and pneumonia, are desirable activities which are not incompatible with the benefits of bed rest. In summary the application of rest as a therapeutic measure requires judgment and individualization; in each case the advantages and disadvantages must be carefully assayed.

Mental Repose. Complete bed rest is ineffective unless there is mental as well as physical repose. The sick room should be quiet and the atmosphere as pleasant as possible. The shades should be drawn when the patient is napping. Visiting hours should be completely restricted at first and limited later. The patient should not be permitted to converse excessively. Upsetting visitors or long discussions should be avoided. Morphine is sometimes necessary the first few days in certain forms of heart failure but later milder sedatives will suffice (see below). However, the indiscriminate administration of narcotics and sedatives is dangerous. Sleep is essential if the rest treatment is to be effective; soporifics should be administered when required. Psychotherapy, including optimism, encouragement and reassurance, will increase the advantages of rest. The patient should not be permitted to become depressed by the thought that going to bed is the end stage of his cardiac disease or by the fear of chronic incapacity. Often it can be honestly stated that complete rest in bed is not a desperate measure of last resort but one of limited duration, utilized prophylactically to prevent more serious symptoms, and to build up cardiac reserve so that the patient can resume his normal or restricted activity.

Modified Bed Rest. If the symptoms of heart failure are mild, e.g., if there is dyspnea only with moderate exertion, it may not be necessary or economically feasible to put the patient to bed for a continuous period. Similarly after a therapeutically successful period of complete bed rest, modification of the restrictions may be permitted. Bed rest may then be tempered with the privilege of leaving the bed for the bathroom or for meals. If the indications are less urgent, the patient may be required to go to bed one or two days a week, usually at the week-end. Or rest periods may be prescribed each day together with early retirement each evening. An hour's rest (in bed if possible) after the noonday and evening meals, an afternoon nap and resting for one to two hours before going out occasional evenings are all desirable forms of partial rest for patients with limited cardiac reserve. In some patients the ability to work during the week is made possible only by staying in bed during the week-end or on Sun-

days. Attacks of nocturnal dyspnea may often be prevented by rest periods during the day.

Convalescence and Exercise. When the maximum benefit has been obtained from bed rest and other measures, the patient is gradually permitted to resume activity, going first through the various stages of modified bed rest discussed above. The rate at which the patient is allowed to return to a more normal life depends on the severity and duration of the attack of heart failure, the response to treatment and other factors in the individual case. It is important to remember that at least some modified form of bed rest is still necessary for a week or two or more after visible evidences of failure, e. g., edema, have disappeared. Daily weighing may reveal a continued loss of occult edema after visible edema has disappeared. Return of symptoms such as dyspnea and orthopnea after getting out of bed for a few days is often an indication of an inadequate period of complete bed rest, which should then be resumed. However, allowance should be made for training needed in the resumption of physical activity. After recovery from an acute episode of congestive heart failure, the patient may gradually resume all his normal activities, especially if failure was due to a specific, determinable cause which was remedied. More often such an episode is followed by a state of limited cardiac reserve so that the patient is comfortable only if his activities are reduced and brief periods of bed rest are intercalated.

Eventually the problem may become one of altering or modifying the patient's work. The business or professional man whose day's work runs from early morning to late in the evening may relieve his symptoms merely by starting later and quitting earlier or by assigning many of his duties to an associate. Frequent vacations or a day's holiday in the middle as well as at the end of the week may be a satisfactory solution. The working man may actually have to change his occupation or he may be able to find less strenuous work with the same employer. A substitution of office or other sedentary duties for tasks involving strenuous physical exertion may be feasible and is desirable, even if income is reduced. These are problems that can sometimes be settled by social service organizations and sometimes by the physician himself with the employer's cooperation. Public education, especially by industrial organizations, in regard to the occupational rehabilitation of the cardiac patient has begun but still has a long way to go.

Women who are ordinarily unemployed and suffer from limited cardiac reserve can usually take longer periods of bed rest or restrict their daily activities more readily than men. The amount of housework should be reduced to a minimum and the more strenuous duties such as shopping, climbing stairs, washing, etc., should be entirely eliminated. This may require either hired assistance or help from children, relatives or friends.

The value of physical exercise for improving the fitness of the heart muscle which has failed has been the subject of varying opinions throughout the last hundred years. Strenuous regimes involving muscular exercises are no longer considered desirable and are probably dangerous for the patient who has recently recovered from heart failure. Mild forms of exercise to improve general muscular tone and circulatory function may be prescribed according to the response of the heart and circulation. As a rule, walking short distances slowly along level ground should be an early form of exercise. The distance and rate

may be gradually increased. Later, simple calisthenics, croquet and a limited number of holes of golf may be attempted. Exercises requiring strenuous competition, speed or endurance or climbing are as a rule interdicted except in rare instances of complete restoration or compensation.

Restriction of Sodium and Fluid. Most of the manifestations of heart failure are due to vascular engorgement and increase in extracellular fluid. Since extracellular fluid retention depends on sodium retention, the control of sodium balance has become a central feature in the strategy of treating heart failure. French clinicians[1, 180, 126] were long aware that patients with heart failure excreted chlorides poorly and that retention of sodium chloride was responsible for edema. It is the sodium and not the chloride ion which is responsible. Ammonium chloride and potassium chloride exert a diuretic action, whereas sodium bicarbonate is as water-retaining as is sodium chloride.

Recent advances in understanding the relationship of sodium and water to heart failure include a much greater emphasis on extreme restriction of sodium intake and less emphasis on the value of fluid restriction. Schroeder[154] showed that limitation of sodium chloride intake to 1.0 gm. a day was usually enough to cause diuresis or prevent edema. But in cases of severe heart failure of long duration it was necessary to reduce the intake of salt to as little as 0.5 gm. per day. As a rule the treatment of congestive heart failure should begin with a sodium chloride intake of no more than 1.0 gm. daily, but the subsequent course may indicate that a more liberal allowance is permissible, without recurrence of evidences of heart failure. Occasionally the requirements of hunger and palatability demand a more generous sodium intake than is ideally desirable, but this may be compensated by the use of diuretics, just as in diabetes a patient may prefer to take insulin rather than further to restrict his food allowance. A more liberal sodium intake may also become permissible if the food to be ingested can be mixed with suitable kationic exchange resins, which withdraw sodium and pass through the intestinal tract without being absorbed.

A sharp limitation in salt intake may be effected by first placing the patient with heart failure on the Karell[97] regime which permits nothing by mouth except 800 cc. of milk daily. This allows about 1 gm. of sodium chloride and 550 calories daily. Even less sodium is obtained if salt-poor powdered milk preparations are used such as Lonalac (Mead Johnson). The advantage of the Karell regime is that it is a simple, fool-proof method of assuring a low sodium diet until control over the patient can be effected, and a more permanent regimen instituted.

After a few days, low sodium diets may be prescribed with more varied foodstuffs, according to the patient's needs. The normal daily diet contains 10 gm. of sodium chloride or more. The salt intake varies between 3 and 6 gm. daily if no salt is added at the table and obviously salt-rich foods are excluded. Further reduction to 2 to 4 gm. daily is effected by omitting all salt from cooking. For stricter sodium-poor diets detailed care is necessary in the choice of foods.

The common sources of sodium are:

1. Salt, added in cooking or at the table. Sodium bicarbonate, bisodol and other sodium-containing medicaments.
2. Bread, crackers, pancakes, salt-containing ready-to-serve cereals, cakes, spaghetti, macaroni.
3. Milk, cheese, salt butter and margarine.

4. Smoked and salt-cured meats and fish, including ham, bacon, salt pork, corned meats, canned meats and fish, and sausages.
5. Bouillon and meat extracts used in soup.
6. Canned vegetables, soups, meat, fish.
7. Spices and condiments, including olives, pickles, catsup, mustard, sauces and salad dressings.
8. Pretzels, popcorn, salted nuts, potato chips, most candies and candy bars.
9. Beets, celery, kale, lima beans, sauerkraut, spinach.

Foods permitted in a low sodium diet include:

1. Fresh fruits(raw or cooked) and fruit juices, canned, dried or frozen fruits or juices (unless label states that salt or sodium benzoate has been added).
2. Fresh or frozen green vegetables without salt. Frozen peas are sometimes salted. The following vegetables are usually permitted.

Asparagus	Corn	Parsley
Beans	Cucumber	Parsnips
Broccoli	Eggplant	Peas
Brussels sprouts	Endive	Radishes
Cabbage	Lettuce	Squash
Carrots	Mushrooms	Tomatoes
Cauliflower	Onions	Turnips

3. Potatoes, rice, cooked cereals prepared without salt. Among the prepared cereals: Puffed rice, puffed wheat, shredded wheat.
4. Passover bread (matzoth), special bread prepared with yeast but without salt and baking powder.
5. Butter—only if unsalted.
6. Milk—limit to two glasses of dialyzed milk (Lonalac). Ordinary milk is relatively rich in sodium.
7. Meat, fish or poultry, prepared without salt, is moderately rich in sodium and should be limited to 3 or 4 ounces.
8. Egg—limit to one daily.
9. Desserts and spreads: Custards, junket, plain puddings using milk and egg from above allowance, fruit pies with unsalted crust, jello, jams, jellies, marmalade and honey.
10. Beverages: Tea, coffee, carbonated drinks, fruit juices, ginger ale, grape juice, coca cola, lemonade.

Drinking water contains a minimal sodium content except in a few cities, or in places where water-softening equipment is used.

Palatability may be increased by seasoning with onions, pepper, lemon, vinegar, curry, mint, parsley, paprika, sage, garlic, pimento, or by flavoring with cocoa, chocolate, coffee, caramel, maple, peppermint, lemon, orange, vanilla, cherries, cloves, cinnamon, nutmeg, ginger.

Sugar is permitted.

Potassium chloride is sometimes substituted for sodium chloride as in Neocurtasal (Winthrop). This is acceptable to some patients but is somewhat bitter and unsatisfactory for most. In the presence of associated renal insufficiency potassium salts should not be administered because of the risk of inducing toxic effects or death from hyperkalemia. Lithium salts, used as sodium substitutes to improve palatability, have been reported to cause serious toxic manifestations and fatalities.[30a, 81b]

Fluid Intake. It has long been the practice to restrict the intake of water by patients suffering from congestive heart failure, especially in the presence of edema. Yet the weight of recent evidence indicates there is no primary impairment in the excretion of water. However, the cardiac patient who is unable to excrete sodium properly and has a positive balance with respect to this ion will also retain fluid in sufficient quantity to keep his extracellular fluid isotonic. In fact, when sodium intake is restricted to minimal levels, the ingestion of plain water even in large amounts serves not to promote water retention and edema but to augment diuresis and to diminish edema.

Recent studies by Schroeder,[154] Schemm,[150] Bridges et al.,[18] Leevy et al.,[106] and Gorham and his associates[79] have demonstrated the effectiveness of *very low* sodium intake in cardiac failure, if at the same time water intake was not restricted. When the diet contained less than 1 gm. of sodium chloride daily, Schroeder observed an occasional increase in diuresis when the patient took generous quantities of fluid and a diminution when fluids were rigidly restricted. Schemm employed a diet containing less than 2.0 gm. daily and claimed beneficial results from forcing fluids to 5000 cc. and over daily.

Gorham et al.[79] observed that with low sodium diets, the net loss of sodium and edema was greater when patients were *encouraged* to take 3000 cc. of fluid daily than when they were restricted to 1500 cc., but little added benefit seemed to accompany the forcing of fluids above 3000 cc. Gorham et al. suggested that the fundamental object was the maintenance of a low sodium intake relative to the water intake rather than a low sodium or high water intake per se, because of the dehydrating effect of hypotonic salt solution.[184] Studies by Crutchfield and Wood[32] of urine volume and total renal sodium excretion during water diuresis disclosed that water diuresis per se increased sodium excretion if the urinary output was previously low. But water diuresis diminished the sodium excretion if the previous urinary volume exceeded 2 to 3 liters daily. These studies and the clinical observations previously mentioned suggest that maximal sodium excretion and urinary output can be obtained when the sodium intake is below 1 gm. daily and the water intake is between 2 and 3 liters daily.

The value of restricting sodium seems apparent in patients with anasarca and serous effusions. Such restriction is believed to interfere with the transudation of fluid from the blood stream into the tissues; it may actually cause a reversal of flow and diuresis. It is equally important to recognize the benefits of salt restriction in patients with left-sided heart failure who have no obvious edema. Attacks of nocturnal dyspnea and cough or of pulmonary edema may be prevented by sodium restriction. In some nonedematous patients with congestive heart failure the presence of extensive occult edema is sometimes indicated by a sharp diuresis and the loss of 5 to 10 pounds in weight when fluids and salt are restricted, usually in combination with other therapeutic measures.

Patients vary greatly in their tolerance of salt restriction. Many become habituated to rigid limitation of salt and suffer no discomfort whether or not substitutes are used. Others react badly with even mild deprivation. Not infrequently the limitation of salt and fluids together with the loss of these substances due to powerful diuretics leads to intense anorexia, weakness, muscle cramps and serious mental symptoms (see p. 196). It may be necessary to increase the sodium allowance in such cases. In some patients extreme sodium restriction and vigorous mercurial diuresis diminish glomerular filtration and

further enhance the renal impairment of sodium-water excretion. A disproportionate electrolyte deficiency may be associated with a salt depletion syndrome and may be benefited by the administration of hypertonic (5 per cent) sodium chloride.[154a]

Diet. Except for the restriction of salt, the diet is not usually a major element in the treatment of congestive heart failure. The two main principles to be followed when there is no contrary indication are: (1) undernutrition and (2) small, frequent feedings. Otherwise the general rules of dietetics are followed. Often the diet is determined by associated conditions such as fever, obesity or malnutrition, avitaminosis, anemia, diabetes.

The benefits of undernutrition result from its reduction of the work of the heart. This is due to the fact, demonstrated by Proger and Magendantz,[141] that dietary restriction causes a sharp decrease in the basal metabolic rate and a significant lowering of the cardiac output, the blood pressure and the heart rate. At the same time the patient's vital capacity is increased and he is able to perform more work. Low caloric diets are especially indicated in obese patients with hypertensive and arteriosclerotic heart disease, particularly when they are confined to bed by symptoms of heart failure. On the other hand, children with cardiac failure and active rheumatic carditis are usually undernourished as are often patients with cardiac failure secondary to avitaminosis. Dietary restriction may be unwarranted or deleterious in such cases. In some cases of heart failure, especially those due to constrictive pericarditis, hypoproteinemia may be severe. A high protein intake appears desirable in such cases. Patients with diabetes and coronary arteriosclerotic heart disease who require insulin therapy should receive an adequate carbohydrate allowance in order to avoid anginal pain due to hypoglycemia (insulin shock).

The total food intake should be divided so as to give small, frequent feedings (five to six times daily). This avoids excessive gastric filling with consequent abdominal distention, elevation of the diaphragm and diminution in vital capacity due to pulmonary compression. Patients who suffer from nocturnal dyspnea, cough or pulmonary edema should take neither food nor fluids after an early evening meal.

The *vitamin content* of the diet should be adequate or supplemented by vitamin concentrates. In particular, vitamin B should be added to the diet by giving thiamine chloride, 5 to 10 mg. daily in divided doses, and brewers' yeast, 4 tablets three times daily. When there is reason to suspect a vitamin B_1 deficiency as a prime or contributing cause of the failure, 20 to 100 mg. of thiamine chloride should be given daily, parenterally, followed after a brief interval by 10 to 20 mg. daily by mouth. Protein and niacin deficiencies often accompany a deficiency of thiamine chloride and these should likewise be corrected.

Palatability of the diet is extremely important. This should be attained by care in the preparation and serving of the food and a choice, as far as feasible, from among those foods which the patient prefers and knows he can tolerate. Usually a *bland, low-residue* diet is better tolerated than one with considerable roughage, since the latter tends to cause distention and flatulence. Cheeses, cabbage, Brussels sprouts and other members of the cabbage family, chocolates, pastries, gravies, fried foods and charged waters should be avoided because of their tendency to cause distention and flatulence. Most patients do not tolerate raw fruits or large quantities of fruit juices which may cause not only distention

but also heartburn and other symptoms of gastric hyperacidity or pylorospasm. Milk should be excluded if it is not well tolerated.

Alcohol. There is no specific objection to the ingestion of moderate quantities of alcohol except in so far as it adds to the caloric intake. Small amounts of sherry, whiskey or brandy are often of benefit, especially to the aged, to those suffering anorexia and weakness and to patients with coronary artery disease and angina pectoris.

Tobacco. There is no clear evidence of harm from smoking, so far as heart failure itself is concerned. If it is too difficult to discontinue the habit, moderate smoking (10 cigarettes or less, or 2 cigars, daily) is permissible provided no unfavorable symptoms are produced. However, if palpitation or extrasystoles occur, if there are heartburn and other evidences of gastric distress, cardiac or epigastric pain, or if the patient suffers from coronary artery disease with angina pectoris, I believe it preferable to discontinue smoking entirely. In my experience, patients find it easier to stop completely than gradually to reduce the number of cigars or cigarettes smoked daily.

Coffee and Tea. There is usually no objection to two or three cups of coffee daily. In fact this may be desirable for patients with coronary artery disease. But if this amount of coffee causes nervous irritability, sleeplessness, palpitation or indigestion, it should be avoided. Sanka or weak tea may be substituted. If strong tea is taken, the same limitations apply as for coffee.

Bowels. A satisfactory daily bowel movement is desirable. Straining at stool must be avoided, especially if the patient suffers from coronary artery disease. There is danger of precipitating an acute coronary occlusion in such patients or of rupturing the heart wall if it is the site of a recent infarction. The risk of pulmonary embolism due to straining has been mentioned. Mineral oil (1 to 2 tablespoons) should be administered each night if the stool is hard. A satisfactory bowel habit may be established if the patient tries to defecate each day at the same time and avoids other times. For the first few days after a coronary occlusion or after the administration of opiates it is preferable to have no bowel movement at all unless this occurs easily and without catharsis. Patients in bed usually require some assistance. Mild laxatives such as milk of magnesia (1 to 2 oz.), cascara sagrada (5 to 10 grains) or compound licorice powder (2 teaspoons) should be given nightly until a soft movement results. Enemas should be given if necessary unless they weaken the patient unduly. I have found a well-given colon irrigation preferable to an enema and better tolerated by the patient.

DIGITALIS AND RELATED DRUGS

Next to rest, digitalis has been the most valuable agent in the treatment of congestive heart failure since Withering[183] in 1785 called attention to the beneficial effect of foxglove on dropsy. In many cases of heart failure the combination of a brief period of bed rest and digitalization suffices to ameliorate or eliminate symptoms. Many patients with limited cardiac reserve are enabled to conduct a somewhat restricted but relatively normal life over a period of many years by the judicious restraint of physical exertion and the maintenance of digitalis therapy.

The Action of Digitalis

The pharmacology of digitalis has been studied extensively (for details see the monographs of Cushny,[33] Weese,[177] Luten,[111] and Movitt[133]) but sev-

eral of the actions of this drug are still obscure. From the viewpoint of clinical application, the following are most important.

Improvement of Myocardial Function. The most important cardiac action of digitalis is a direct beneficial effect on myocardial contraction. The digitalis glycosides enter the myocardial cells where they yield active aglycones which, in some unknown manner, produce a more forceful systolic contraction of the heart. This has been repeatedly demonstrated experimentally in strips of heart muscle, the isolated heart and the heart-lung preparation.[33, 30] Schaefer,[149] using the heart-lung preparation, demonstrated more forceful ventricular contraction and more complete emptying; the digitalized heart could expel its contents against a significantly higher arterial resistance than could the undigitalized heart. More recently Cattell and Gold,[23] using the isolated papillary muscle of the cat, and Kabat and Visscher,[96] using the tortoise heart, similarly demonstrated striking increases in the force of systolic contraction and the work capacity of the heart muscle, respectively, following the administration of digitoxin, ouabain, or K-strophanthoside.

Digitalis not only increases the force of systolic contraction, the capacity of the heart for work and the completeness of ventricular emptying, but also enhances the efficiency of myocardial contraction. For Gremels,[81] using the heart-lung preparation, noted that following the administration of strophanthin, the heart utilized less oxygen for a given amount of work. Similar observations of Peters and Visscher[138] and Moe and Visscher[132] also indicated that digitalis bodies increase cardiac efficiency, so that a greater percentage of energy expended is converted into external work. In other words, digitalis increased the amount of mechanical work developed at a given oxygen expenditure—a reversal of the basic energy disturbance in myocardial failure.[104, 50]

Because of these observations and others to be discussed below, it appears probable that the major benefit of digitalis in heart failure is due primarily to its improvement in cardiac contraction and efficiency, and only secondarily in certain cases to slowing of the heart rate. Thus, in cases with regular sinus rhythm, digitalis may lead to clinical improvement of heart failure without concomitant slowing of the heart rate, or before such slowing occurs. Furthermore, although there is no direct conclusive evidence in humans, such a myocardial action of digitalis has better experimental support and is more consonant with known observations than the suggested hypothesis of an extracardiac (peripheral vascular) action. We have seen that the signs and symptoms of congestive heart failure and their localization are ultimately determined by the inability of a failing chamber to handle the venous return, especially when this is increased during activity. By augmenting the force of cardiac contraction and improving myocardial efficiency, digitalis enables the venous return to be accepted and ejected, reduces the elevated venous pressure, increases the cardiac output and restores compensation.

Slowing of the Cardiac Rate. The rate of the heart is commonly accelerated in congestive heart failure, but this acceleration is especially pronounced and significant in those cases in which failure is associated with auricular fibrillation. In the latter group especially, digitalization rapidly effects a reduction in the ventricular rate to normal levels; concomitantly there is usually a striking amelioration in the clinical manifestations of heart failure. Slowing of the heart by digitalis glycosides may be mediated by (a) vagal stimulation or (b) direct myocardial action on the atrioventricular node and bundle whereby atrioventricular conduction is depressed.

Vagal Stimulation. That digitalis produces slowing of the heart through vagal stimulation is indicated by observations, both in animals and man, that such slowing is diminished or abolished by vagotomy or the administration of atropine.[33] The vagal component is dominant with early therapeutic doses, for Gold and his associates[75] showed that atropine increased the ventricular rate in auricular fibrillation after it had been slowed by digitalis. But after full digitalization, the rate could no longer be accelerated by atropine, presumably because with larger doses slowing was mediated by extravagal means.

The exact method by which digitalis induces vagal slowing of the heart is uncertain. Heymans and his co-workers,[91] in cross-circulation experiments, slowed the heart rate of dogs by perfusing the carotid sinus with digitalis. Similar perfusion of the vagus center produced no slowing if the center was isolated from the afferent sinus nerves. These experiments suggested that digitalis slowing was effected by action of the drug on the perceptors of the carotid sinus with a consequent reflex increase in vagal tone, and a diminution of the rate of impulse formation in the sinoauricular node.

However, there is more evidence that this reflex vagal effect, at least in congestive heart failure, is not due to direct action of digitalis on the sinus receptors, but to afferent stimuli initiated when the failing heart muscle is restored to compensation by direct myocardial effects of digitalis. In persons with normal hearts digitalis causes slight or no slowing except with toxic doses. Digitalis reduces the cardiac rate in tachycardias only when the tachycardia is due to heart failure. In patients with auricular fibrillation digitalis induces striking slowing of the heart when there is associated heart failure but little or no ventricular slowing in cases of auricular fibrillation without heart failure. All these observations seem to support the concept that digitalis in therapeutic doses exerts its slowing effect essentially in the presence of failure, and that the reduction in cardiac rate is secondary (by way of vagal reflexes) to the digitalis-induced improvement in myocardial function.[111]

That tachycardia is a compensatory reaction to cardiac failure has been discussed. Presumably the tachycardia is initiated by an elevation of venous pressure with a consequent Bainbridge reflex. Elimination of this tachycardia requires abolition of the myocardial failure which induced the increase in heart rate. By causing a more forceful cardiac contraction and more complete emptying, digitalis relieves the heart failure, reduces the venous pressure and abolishes the reflex responsible for the compensatory tachycardia.

Depression of Atrioventricular Conduction. Digitalis impairs the conduction of impulses from the atrium to the ventricle partly by vagal stimulation but also and predominantly through the direct action on the junctional conduction tissues. This occurs both in healthy and decompensated hearts and is disclosed electrocardiographically by prolongation of the P-R interval and with more toxic doses by more severe degrees of atrioventricular heart block. Lewis and his co-workers[109] demonstrated a digitalis-induced inhibition of atrioventricular conduction, even when vagal depression was excluded by atropine, in dogs in which the atria were stimulated to produce a rapid auricular rate as in fibrillation.

According to Mackenzie[115] and to Lewis,[110] depression of atrioventricular conduction by digitalis accounts for its usefulness in cases of auricular fibrillation with rapid ventricular rate, in which the drug's most striking benefits are clearly demonstrable. When the atria fibrillate, they may discharge 400 or

more impulses per minute, to which the harried ventricles may respond with 100 to 160 contractions per minute. But these ventricular contractions are less efficient than normal because (a) the diastolic recovery period is diminished by the tachycardia and (b) the auricular impulses arrive so rapidly and irregularly that many ventricular contractions occur too soon after the previous one to permit adequate filling or expulsion of blood. Therefore many of the ventricular contractions are too weak to open the aortic valve or produce a palpable radial pulse (pulse deficit).

According to the Mackenzie[115] concept digitalis by impairing atrioventricular conduction diminishes the frequency of impulses bombarding the ventricles and thereby slows the ventricular rate. Consequently more effective systolic contraction and emptying are possible, the pulse deficit is eliminated and compensation restored. According to Luten and Jefreys,[112] the digitalis effect on atrioventricular conduction is of secondary importance in accounting for myocardial improvement in cases of auricular fibrillation and heart failure. As stated above, clinical improvement is attributed to direct action of digitalis on the myocardium with stronger cardiac contraction. The ventricular slowing is then due (a) partly to vagal reflexes as myocardial function improves, and (b) to increase in the refractory period of the ventricular myocardium due to its stronger contraction, thereby rendering the heart muscle unresponsive to most of the auricular impulses. According to this explanation, increased myocardial refractoriness due to more forceful contraction is more important than impaired atrioventricular conduction in explaining the digitalis effect in cases of auricular fibrillation with heart failure.

Peripheral Action of Digitalis. The possibility that the beneficial effect of digitalis in congestive heart failure is due essentially to a peripheral action[45, 123] whereby the venous return is diminished by venoconstriction is discussed below under the heading Cardiac Output and Venous Return.

Digitalis and Cardiac Size. There is uniform agreement that in the heart-lung preparation in normal animals, in normal persons and in patients with congestive heart failure, digitalis reduces the size of the heart.[30, 163, 104] Cardiac failure is associated with an enlarged heart which, as shown by Starling and Visscher,[162] is inefficient because it consumes relatively more oxygen than the normal heart for the performance of the same amount of useful work. By diminishing the size of the dilated decompensated heart digitalis increases its fitness or functional capacity so that it carries out its work with a lesser volume, a lesser oxygen consumption and therefore with greater efficiency.

On the other hand one must not mistake cause and effect. The development of cardiac enlargement in congestive heart failure is a compensatory mechanism by which the fatigued and damaged heart attempts to maintain an adequate output. Conversely, reduction in size of the enlarged heart by digitalis may not be a direct effect of digitalis but rather a reversal of the process of dilatation as the digitalis promotes the strength and efficiency of myocardial contraction. Consequently less compensatory enlargement is necessary than before digitalization. The experiments of Cattell and Gold[23] indicate that digitalis acts directly on the heart muscle to increase the tension which it can develop during systolic contraction, without a primary change in the diastolic length of the muscle. In addition to the direct benefit of digitalis for the heart muscle, the secondary reduction in heart size is itself advantageous because of the lesser oxygen requirement and the greater efficiency of cardiac contraction.

Digitalis and Circulatory Dynamics. The clinical benefit of digitalis in heart failure has been shown to be based primarily on its direct improvement of myocardial contraction and efficiency and in part or secondarily on slowing of the cardiac rate. In addition digitalis tends to restore to normal the various aberrations in circulatory dynamics which develop in the course of heart failure. These effects, like the reduction in cardiac size, are probably not direct consequences of digitalis activity but secondary to strengthening of cardiac contraction and enhanced cardiac emptying.

Cardiac Output and Venous Return. In the heart-lung preparation digitalis may produce a temporary increase in cardiac output after the heart dilates.[138] But in normal dogs, in dogs with compensated valvular lesions and in normal men, digitalis reduces the cardiac output.[84, 30, 21, 45, 163]

In cases of heart failure, Stewart and his associates[163] observed an almost constant increase in cardiac output following digitalization. More recently, McMichael and Sharpey-Schafer,[124] using the method of intracardiac catheterization, observed striking and uniform augmentation of cardiac output following the administration of digitalis to patients with congestive heart failure. Bloomfield et al.,[11] using the same technic, observed a uniform increase in cardiac output (due to increase in stroke volume) following the intracardiac administration of 0.25 to 0.75 mg. of ouabain.

To account for the diminished output of normal hearts following digitalization, Dock and Tainter[45] concluded that digitalis caused a diminution in the venous return, probably by a constriction of the hepatic veins. This was based on the observations in dogs that digitalis caused not only a diminution in cardiac output but also a simultaneous reduction in venous pressure and an increase in the volume of the liver and of the portal venous pressure. However, an hepatic venoconstrictor (throttle) mechanism such as occurs in the dog could not be demonstrated in humans.[3]

McMichael and Sharpey-Schafer[124] likewise concluded that digitalis exerted a peripheral venoconstrictor action in congestive heart failure, for the *increase* in cardiac output and fall in venous pressure mirrored closely similar changes produced by venesection or by the application of tourniquets. They concluded that digitalis, by causing venoconstriction, diminished the venous return and thus enabled the overloaded heart to contract more efficiently and augment its cardiac output. But with respect to congestive heart failure, the digitalis-induced enhancement in cardiac output and fall in venous pressure can be more satisfactorily explained by the direct myocardial action of digitalis with consequent improvement in cardiac contraction and emptying. With respect to the reported diminution in cardiac output following digitalization of normal hearts it is probable that this is related to a reduction in blood volume and venous return, but it is unnecessary to assume a digitalis action on the peripheral veins. Here too, a direct myocardial effect may be primary with subsequent increase in renal excretion of sodium and water, diminution in blood volume and reduction in the venous return.

Circulating Blood Volume. Digitalis diminishes the circulating blood volume both in normal individuals[129] and in subjects with congestive heart failure.[155] We have seen that the increased blood volume in congestive heart failure results from renal retention of sodium and water and serves as a compensatory mechanism designed to restore a deficient cardiac output. Digitalization, by improving cardiac contraction and cardiac output, reverses this series of events and diminishes the blood volume.

Venous Pressure. The venous pressure is diminished after the administration of digitalis to patients with heart failure.[48, 185a] This is best explained by improvement in cardiac contraction and emptying, whereby the venous return is more effectively handled and damming of blood in the inflow veins to the failing chamber is eliminated. In the observations of Bloomfield et al.[11] an improvement in cardiac output preceded any fall in venous pressure. In cases of isolated left ventricular failure Ferrer et al.[54a] observed that the administration of digoxin was followed by an augmented cardiac output and a sharply reduced pulmonary artery pressure, but there was no effect on the central venous pressure.

Circulation Time. The circulation time of normal patients is not affected by digitalis. But in patients with congestive heart failure the prolonged circulation time is diminished.[163, 104]

Digitalis and Electrolyte Excretion and Renal Function. Digitalis produces a prompt increase in the excretion of sodium and water in patients with congestive heart failure.[45b] There is an enhanced renal plasma flow and glomerular filtration, and a diminution in the filtration fraction and renal venous pressure. However, the improvement in excretion of sodium and water is not distinctly related to changes in glomerular filtration.

Indications for Digitalis Therapy

1. Congestive heart failure, with regular sinus rhythm or with auricular fibrillation. This is the primary indication for digitalis.
2. Auricular fibrillation, especially when the ventricular rate is rapid and congestive heart failure is present.
3. Auricular flutter.
4. Prevention and treatment of recurrent episodes of paroxysmal auricular tachycardia.

Congestive Heart Failure. Digitalis is indicated primarily and most frequently in the treatment of congestive heart failure due to myocardial strain or impairment, regardless of etiology. Digitalis is indicated whether heart failure is mild or severe, whether the rhythm is regular or irregular and whether or not heart block (unrelated to digitalis) is present. In cases of heart failure in which some known remediable factor is the precipitating cause, e. g., infection, anemia, hyperthyroidism, correction of the precipitating factor may be more important, but the administration of digitalis is also indicated at least until heart failure is abolished.

Heart Failure with Auricular Fibrillation or Flutter. The most dramatic therapeutic effects of digitalis are observed in cases of heart failure and auricular fibrillation, especially when the ventricular rate is so rapid as to impair ventricular filling or cut into the recovery phase of diastole. With digitalization ventricular rates of 120 to 150 may be rapidly reduced to 60 to 80 per minute, and a pulse deficit is eliminated. Concomitantly the manifestations of congestive heart failure such as dyspnea or venous engorgement are ameliorated or annulled. If palpitation, precordial distress or weakness is due to the rapid irregular ventricular rate, these symptoms are relieved as the rate is slowed by digitalis.

Digitalis should be administered to patients with congestive heart failure and auricular fibrillation even though the ventricular rate is not rapid. The essential purpose of digitalization in cases of congestive heart failure is the improvement

of the function of the myocardium and not the modification of the ventricular rate. The prophylactic use of digitalis in cases of compensated heart disease with auricular fibrillation and slow ventricular rate, in order to delay or prevent heart failure, also has its adherents.[25]

Digitalis often exerts striking therapeutic effects in patients with heart failure and auricular flutter. Frequently the digitalis not only slows the heart but converts the auricular flutter into auricular fibrillation. Although stoppage of digitalis may be followed by restoration of regular rhythm, this is unlikely to occur and the digitalis should not be discontinued for this purpose in cases of organic heart disease with enlarged hearts and chronic heart failure.

Heart Failure with Regular Rhythm. The value of digitalis is usually less striking in cases of heart failure with regular rhythm than in those with auricular fibrillation; nevertheless its benefit is sufficiently clear.[25, 111, 118, 87, 54, 57] Gavey and Parkinson[66] found digitalis efficacious in more than half of 47 cases of congestive heart failure with sinus rhythm, and concluded that digitalis was indicated in the treatment of congestive heart failure, irrespective of the rhythm. In many of the observations made in patients with heart failure and regular rhythm, digitalis reduced the cardiac rate, without notable clinical benefit; in others clinical improvement occurred without a change in the heart rate; but in general clinical benefit and slowing of the heart occurred concomitantly. Flaxman[57] reported that digitalis was more effective in cases of heart failure with normal rate than in those with sinus tachycardia. He concluded that the beneficial action of digitalis was on the myocardium and not on the ventricular rate.

In a recent study by Wood,[185] digitalis effected demonstrable improvement in 18 of 20 patients with congestive heart failure and normal rhythm. Repeated determinations of the venous pressure were utilized to evaluate progress in his cases of right-sided heart failure, and the arm-to-tongue circulation time in his cases of left heart failure. He likewise observed that a diminution in the cardiac rate was usually associated with improvement from digitalis therapy, but in 2 cases there was no such alteration in rate despite distinct benefit. It is clear from these and other studies that digitalis produces clinical improvement in congestive heart failure by direct beneficial action on the heart muscle which is independent of its effect on cardiac rhythm or slowing of the cardiac rate.

The beneficial effect of digitalis is not limited to cases of right heart failure with venous congestion, hepatic enlargement and peripheral edema. Some of the most striking results are obtained in patients with isolated left-sided failure.[57] Thus, dyspnea on exertion or at rest, orthopnea, cardiac asthma, nocturnal cough when due to the pulmonary congestion of heart failure, are all indications for the administration of digitalis. In a series of cases of pure left-sided heart failure, Harrison, Calhoun and Turley[83] found that digitalis relieved the dyspnea and attacks of cardiac asthma and concomitantly increased the vital capacity and the speed of circulation.

Auricular Fibrillation (See also p. 278). Digitalis is most clearly indicated and is particularly beneficial in those cases of auricular fibrillation and rapid ventricular rate which are associated with congestive heart failure. Usually these are cases of arteriosclerotic and hypertensive heart disease or of rheumatic heart disease with mitral stenosis. It is still a moot question whether the striking efficacy of digitalis in these cases is due exclusively or essentially to direct improvement in the efficiency of the failing myocardium,[112, 104] or in large measure to indirect improvement mediated by impairment of atrioventricular conduction

and consequent ventricular slowing. Digitalis does not abolish auricular fibrillation; in fact its direct or reflex effect on the vagus nerve, by reducing the refractory period of atrial muscle, tends to perpetuate fibrillation (p. 278).

When digitalis reduces the ventricular rate to between 60 and 80 per minute in cases of auricular fibrillation and heart failure, it must be continued in the dosage necessary to maintain the desired ventricular rate and other clinical effects. However, auricular fibrillation with normal or slow ventricular rate is sometimes encountered in the absence of heart failure. There are usually no symptoms and there is no indication for digitalis.

When auricular fibrillation with rapid ventricular rate is due to hyperthyroidism alone, digitalis is not indicated. Neither is it indicated in the cases of auricular fibrillation due to a variety of less common causes of toxic, traumatic, infectious, neoplastic or other origin (p. 274).

Auricular Flutter (See also p. 271). Digitalis is indicated in cases of congestive heart failure associated with auricular flutter, and in cases of auricular flutter with organic heart disease and pronounced enlargement of the atrium or ventricles. Digitalis is also indicated in cases of auricular flutter without heart failure or cardiac enlargement, which have failed to respond to quinidine therapy.

The digitalis does not abolish auricular flutter but tends to convert it into auricular fibrillation by shortening the refractory period of auricular musculature. Large doses of digitalis are required and mild atrioventricular block may be produced. In most cases without serious organic heart disease, discontinuance of digitalis when auricular fibrillation has developed is followed by a reversion to regular sinus rhythm. If auricular flutter recurs repeatedly or if auricular fibrillation persists, digitalis therapy may have to be continued in order to maintain optimal slowing of the ventricular rate.

Paroxysmal Tachycardia. The initial therapeutic measures recommended for the control of paroxysmal auricular tachycardia are discussed elsewhere (p. 264). If carotid sinus pressure, other vagal reflexes, mecholyl, potassium salts or quinidine have failed to control an attack of paroxysmal tachycardia and especially if heart failure ensues, digitalization may be effective and should be given. Preparations for intravenous injection (ouabain, cedilanid, etc., p. 187) should be used if rapid action is important.[160] Digitalis glycosides have also been recommended for prophylactic use in the prevention of recurrent paroxysmal arrhythmias.

Factors Modifying the Indications for Digitalis

Digitalis has been found to be more effective in certain cases of congestive heart failure or auricular fibrillation than in others. Such apparent discrepancies will be clear if the actions of digitalis are kept in mind. For digitalis can be beneficial only if the symptoms are due either to impaired myocardial function which can still be helped by the drug or to ventricular tachycardia secondary to auricular fibrillation which can be slowed by impairing atrioventricular conduction. Thus digitalis is ineffective in cases of cardiac failure due to *mechanical impediments* such as constrictive pericarditis, extreme mitral stenosis or auricular thrombi occluding the mitral orifice. It is also ineffective when myocardial damage is too severe or extensive to permit the heart muscle to respond to the medicament. Digitalis is often of little help when the causative factor of heart failure is still active, e. g., active rheumatic fever, diphtheria, Graves' disease,

myxedema, avitaminosis, severe anemia or arteriovenous aneurysm. In such cases medical or surgical elimination of the cause should be the essential element in therapy, and digitalis only an accessory.

Contraindications and Non-indications for Digitalis Therapy

Arrhythmias and Tachycardias. Digitalis is not indicated for the treatment of tachycardias due to infections or fevers, to hyperthyroidism, drugs, or neurocirculatory asthenia unless congestive heart failure is present. Digitalis has been said to be contraindicated in the presence of premature contractions because of the danger of producing ectopic beats, but the latter result only from toxic doses of the drugs. If cardiac failure appears, the coexistence of premature beats does not contraindicate the use of digitalis. Sometimes digitalis appears to dispel protracted premature beats with or without associated heart failure. Similarly digitalis may occasionally terminate a prolonged paroxysmal tachycardia.

Conduction Disturbances. Digitalis has frequently been said to be contraindicated in cases of *partial heart block* because of the danger of further impairment of atrioventricular conduction and the consequent development of complete heart block. On the other hand, Eggleston[47] obtained satisfactory results with the use of digitalis, the block sometimes disappearing when heart failure was relieved. In a recent study of 19 patients with various grades of heart block, most of whom were suffering from congestive heart failure, Blumgart and Altschule[12] administered digitalis in sufficient dosage to produce a therapeutic effect without observing any increase in the degree of block. In some cases the P-R interval was shortened as the patient improved under digitalis therapy.

In patients with *complete heart block,* digitalis is indicated only if there is congestive heart failure. In the latter cases good therapeutic effects may be obtained with improved myocardial function. The degree of block cannot be further increased. However, because of its vagal action, digitalis may be undesirable in patients with frequent Adams-Stokes attacks or carotid sinus hypersensitivity.[134]

Digitalis is not indicated in cases of sinus arrhythmia, sinoauricular block, nodal rhythm or ventricular escape, except when associated with heart failure. These arrhythmias are often due to digitalis toxicity.

Coronary Artery Disease. Coronary artery disease with angina pectoris or recent coronary occlusion is in itself neither an indication nor a contraindication to the use of digitalis. Reports of the development or exacerbation of cardiac pain following the administration of digitalis[69, 60] have led to hesitancy in using the drug in patients with angina pectoris for fear of causing vasoconstriction of the coronary arteries. Freedberg and his associates[60] called attention to the similarity between the electrocardiographic changes associated with angina pectoris and those induced by digitalis. But there is no definite evidence that therapeutic doses of digitalis have a significant direct effect on coronary blood flow.[70, 51] Furthermore, Gold, Otto and associates,[76] in a study of 120 patients with angina pectoris who were treated by alternating courses of digitalis and a placebo, concluded that digitalis medication does not produce cardiac pain. The beneficial effect of digitalis on the heart rate and efficiency of cardiac contraction in cases of heart failure should serve indirectly to promote the coronary blood flow, for the coronary flow is augmented in proportion to the

work of the heart when the rate is slowed and the stroke volume increased (p. 324). Digitalis should be given to patients with heart failure even if they suffer from angina pectoris.

Similarly digitalis is not contraindicated if congestive failure develops in a patient with an acute coronary occlusion (coronary thrombosis) (p. 493).

Shock and Infection. Digitalis is contraindicated in cases of central or peripheral circulatory failure associated with shock. Digitalis further reduces the low blood volume and the insufficient output of the heart. Postoperative shock is an example of a condition in which digitalis continues to be employed without benefit and probably with harm to the patient. Digitalis is not indicated in cases of circulatory shock accompanying infections such as pneumonia or diphtheria. A controlled study of a series of 834 cases of lobar pneumonia, in which alternate patients were given digitalis, revealed a slightly higher mortality in the digitalized group.[186] In cases of rheumatic fever digitalis is not indicated, but when congestive heart failure appears the drug should be administered. As a rule the benefits are not striking if there is rheumatic activity and large doses of the drug are required.

Surgical Procedures. Digitalis has been used extensively and unjustifiably in many patients who undergo surgical procedures. There is no proof of its value preoperatively unless congestive failure is already present or unless the patient is subject to frequent attacks of paroxysmal auricular fibrillation, one of which may be precipitated by the operation. Following operation, digitalis is not indicated either for cardiovascular collapse (shock), tachycardia or premature beats, all of which occur frequently.

Hypertension and Nephritis. Hypertension is no contraindication to the use of digitalis in the treatment of heart failure. An elevated blood pressure associated with heart failure *(Stauungshochdruck)* may fall when digitalis relieves the failure. On the other hand, cardiac failure may be accompanied by a drop in blood pressure which increases again when the heart recovers after digitalis therapy. Digitalis is also well tolerated in patients with nephritis associated with congestive heart failure.

Prophylactic Use of Digitalis. Christian[25] has urged the prophylactic use of small doses of digitalis in patients with compensated, enlarged hearts which are likely to fail sooner or later. He believes such therapy inhibits further cardiac enlargement as well as congestive heart failure. In the absence of adequate evidence to support this concept, I do not give digitalis prophylactically to patients with compensated heart disease, unless digitalis was previously employed during heart failure.

Toxic Symptoms. The chief contraindication to the administration of digitalis is the presence of symptoms due to overdosage of this drug (see p. 189).

Preparations, Standardization and Dosage of Digitalis

Powdered Whole Leaf. Until recently the powdered whole leaf of digitalis was the preparation recommended by the Digitalis Committee of the American Heart Association and it is probably still used most widely. It is a galenic preparation obtained from the dried leaves of Digitalis purpurea, in the second year of growth of the plant, and administered in the form of tablets, capsules or tincture, and rarely in suppositories or infusions. The tablets, pills and capsules usually contain 0.1 gm. (1½ grains or 1 cat unit) each, and possess the advantage of accurate dosage and convenience of administration. The tincture

of digitalis, which is a 10 per cent alcoholic solution of the leaf, has also been used extensively and will not deteriorate for a long time if kept in a properly stoppered bottle. An accurate minim dropper is essential for measuring the dose.

Dosage of Powdered Leaf of Digitalis. The digitalizing dose is about 1.2 to 2.0 gm. of U.S.P. XIII digitalis leaf or 12 to 20 cc. of the tincture. The subsequent maintenance dose is 0.1 to 0.15 gm. or 1.0 to 1.5 cc. of the tincture. Details of digitalization and maintenance are discussed below.

Absorption of digitalis leaf is relatively poor, i. e., only about one fifth of the administered dose. About 0.1 to 0.2 gm. is excreted daily after full digitalization.

Digilanid. Effective digitalis glycosides can be obtained from the leaf of Digitalis lanata as well as the more commonly employed Digitalis purpurea. The essential ingredients of Digitalis lanata and their approximate proportions are: lanatoside A—46 per cent; lanatoside B—17 per cent; lanatoside C—37 per cent. Digilanid is a preparation of constant composition, in which the impurities of the crude leaf have been removed and the pure active lanatosides A, B and C have been combined in the above percentages. It is provided in 0.33 mg. tablets = 1 cat unit.

Dosage of Digilanid. The digitalizing oral dose ranges between 3.0 and 8.0 mg. with daily doses of 0.33 mg. for maintenance. The intravenous digitalizing dose is 3.0 mg.

Digitoxin and Other Pure Digitalis Glycosides. Digitoxin is a relatively pure crystalline digitalis glycoside isolated from digitalis leaf by Schmiedeberg[152] in a more purified form than the digitaline crystallisée of Nativelle. Digitoxin, gitoxin and gitalin are the glycosides obtainable from Digitalis purpurea leaf. Digitoxin can also be obtained by hydrolysis of lanatoside A and gitoxin from lanatoside B of the Digitalis lanata leaf. Lanatoside C yields digoxin which is unobtainable from Digitalis purpurea. The chief advantage of digitoxin and other digitalis glycosides is their uniform and constant potency which makes it possible to administer them by weight and eventually dispense with biological assay. The toxic symptoms of overdosage with cardiac glycosides are identical with toxic symptoms caused by the whole leaf preparations.

Digitoxin is completely absorbed from the intestinal tract as indicated by the fact that the digitalizing dose is identical whether the drug is given orally or intravenously.[173] There is no nausea or vomiting due to local gastric irritation but central nausea occurs with excessive dosage of digitoxin as with other digitalis preparations.[71] The absence of gastrointestinal disturbance is attributed to freedom of the drug from irritating impurities, rapid and complete absorption and the minute dosage required for therapeutic effectiveness. Compared to other glycosides digitoxin has a relatively long patent period, possibly due to its fixation to blood proteins.[168] Its activity begins one hour after intravenous administration and its maximum effect requires four hours or longer. The chief disadvantage is its long period of dissipation, two to three weeks being required for elimination. Therefore, when toxic symptoms appear, they are relatively persistent. On the other hand, the slow elimination of digitoxin may also be considered an advantage because digitalization can be readily maintained for a long time.

Dosage of Digitoxin. The digitalizing dose is 1.2 mg. when given in a single

dose,[72] but many patients require up to 2.0 mg.[167, 39] I have repeatedly observed toxic symptoms with the lesser dose (1.2 mg.). The average daily maintenance dose is stated to be 0.2 mg., but often 0.1 or 0.15 mg. or as little as 0.05 mg. suffices. It is apparent that digitoxin is approximately 1000 times as powerful as digitalis leaf, i. e., 0.1 mg. digitoxin = 0.1 gm. digitalis leaf.

Dogmatic oversimplification of dosage directions has lent unusual appeal to this preparation and has resulted on the one hand in inadequate digitalization in some patients, and on the other in toxic manifestations in other patients who require less than the recommended dose of 1.2 mg. Thus DeGraff and his associates[39] found that only 17 per cent of patients were satisfactorily digitalized with 1.2 mg. of digitoxin, and that 1.7 mg. was the average single therapeutic dose. At the same time I have observed a pronounced increase in the occurrence of digitalis toxicity since digitoxin has been administered in the prescribed fixed dosage of 1.2 mg. Flaxman[58] recently reported 30 cases of digitoxin poisoning in patients who had taken the recommended doses of the drug. The earliest and commonest symptoms were disturbances in conduction, including prolongation of the P-R interval and a-v dissociation. Master[120] described 9 cases of digitoxin poisoning with gastrointestinal and psychic symptoms, arrhythmias, auricular, nodal and ventricular tachycardia, partial and complete heart block and electrical alternans.

Digoxin. This is a pure crystalline glycoside derived from the leaves of Digitalis lanata and is closely related to lanatoside C. Like digitoxin it is a pure substance of definite and constant composition which can be prescribed in terms of weight of the pure drug. Its pharmacologic effects are identical with those of the whole leaf of digitalis or any of its glycosides.[176, 148]

According to DeGraff,[37] digoxin, like digitoxin, is thoroughly and quickly absorbed from the gastrointestinal tract, but there is some uncertainty regarding this point. Digoxin is rapidly eliminated from the body, which bears the advantage of less likely and briefer toxicity, but also the disadvantage of greater difficulty in maintaining continuous digitalization. Elimination of a full digitalizing dose is complete in about forty-eight hours if no further digitalis has been given.[5] Therefore if there is uncertainty as to recent digitalis intake, digoxin may be safer to administer than other digitalis preparations.

Dosage of Digoxin. The average digitalizing dose of digoxin given within twenty-four hours is about 3.75 mg. with a range of 2.0 to 5.0 mg.[37, 53] Because of its more rapid elimination, the daily maintenance dose is 0.5 mg. to 0.75 mg. compared to 0.2 mg. for digitoxin. Because of low solubility in water, digoxin is prepared for intravenous use in alcoholic solution, which must be diluted with saline before use. In the rare instances in which digitalis must be given intravenously, other digitalis preparations are preferred (p. 187).

Lanatoside C. Lanatoside C, marketed under the trade name Cedilanid, is an initial crystalline glycoside, related to digoxin and likewise derived from Digitalis lanata leaf.[165] Compared with the other two commonly employed glycosides already discussed, lanatoside C has the shortest latent period and the most rapid elimination. The speed of elimination makes it less satisfactory than digitoxin for oral use, because it is difficult to maintain digitalization, and relatively high initial dosage is required. On the other hand the brief latent period makes lanatoside C desirable for intravenous administration.[54, 160] Slowing of a rapid ventricular rate in auricular fibrillation may be effected

within ten minutes to two hours after intravenous administration. Its effect persists twelve to thirty-six hours and disappears in three to six days.[49] In summary, lanatoside C is more rapid in its effect than digitoxin, slightly more rapid than digoxin, but slower than ouabain (below). Therefore it is not as immediately effective as the latter for urgent intravenous use, but the duration of its effect is longer.

Dosage of Lanatoside C. The average oral digitalizing dose of lanatoside C is 7.5 mg. (5.0 to 10.0 mg.) within twenty-four hours.[71, 160] Maintenance dose is 1.0 to 1.5 mg. daily. For rapid intravenous digitalization the dose is 0.8 mg. to 1.6 mg. lanatoside C, given slowly or in divided doses every four hours until the desired effect is attained. The maintenance dose intravenously is 0.4 mg. every six hours. Lanatoside C is available commercially as Cedilanid in tablets of 0.5 mg. and in ampules of 2 cc. containing 0.4 mg. and in ampules of 4 cc. containing 0.8 mg.

Ouabain and Other Strophanthins. A number of glycosides have been isolated from Strophanthus kombé and Strophanthus gratus.[101] The most important of these is ouabain, a pure crystalline substance derived from the latter. Both ouabain and the various K strophanthins, now available, are poorly absorbed from the gastrointestinal tract and therefore unsuitable for oral use.

Ouabain (G strophanthin) is the drug of choice for emergency intravenous use because of its very brief latent period.[24] A reduction in ventricular rate and venous pressure may be attained within five minutes after injection, with a maximum effect in thirty to 120 minutes and a duration of twenty-four to seventy-two hours.[48, 71] Its rapid elimination makes ouabain unsatisfactory for maintenance of digitalization. Therefore the combined use of ouabain intravenously for rapid immediate effect with digitalis preparations orally for subsequent maintenance has been recommended.[6] According to Kwit[102a] acetyl strophanthin acts even more rapidly than ouabain, producing its full effect in ten minutes as compared to one hour for the latter.

Dosage of Ouabain. The average digitalizing dose for ouabain is 0.8 to 1.0 mg. which should be given intravenously in divided dosage. After an initial dose of 0.5 mg., 0.1 mg. doses may be given every half hour or hour until the desired effect is obtained. Ouabain is available in 0.5 cc. ampules containing 0.1 mg., and 2 cc. ampules containing 0.5 mg.

Other Digitalis-like Preparations—Squill. Glycosides of squill also have a satisfactory digitalis-like action and have been used therapeutically. The commercial preparation Scillaren contains 2 parts crystalline scillaren A and one part of amorphous scillaren B. One commercial preparation urginin (Urginea Indica) has two water insoluble glycosides urginin A and B, while another urginin (from Urginea Maritima) contains equal mixtures of scillaren A and B. The digitalizing dose is 9.0 to 14.0 mg. for scillaren and 4.0 to 6.0 mg. for urginin. The daily maintenance dose is about 0.8 mg. for urginin and 1.6 mg. for scillaren.

Still other preparations with a digitalis-like action, but not recommended for clinical use, include cymarin from apocynum, thevetin, a cardiac glycoside obtained from the nuts of the be-still plant, convallaria, and folinerin—a crystallized glucoside from the Nerium oleander. Analysis of the various commercial preparations and their therapeutic effects have been reported by Stroud and VanderVeer,[167] Evans,[52] DeGraff,[37] and Freedberg and Zoll.[61]

Standardization and Assay of Digitalis Preparations

According to U.S. Pharmacopoeia XIII the potency of digitalis is such that when assayed as directed 0.1 gm. shall be equivalent to not less than 1.0 U.S.P. digitalis unit. One U.S.P. digitalis unit represents the potency of 0.1 gm. of the U.S.P. Reference Standard. This latter in turn is standardized according to a standard international reference powder of digitalis. In actual usage digitalis preparations for intravenous injection containing a given number of digitalis units may have a much greater pharmacologic effect than digitalis leaf preparations with the same number of units administered orally. This is largely due to less and variable absorption from the gastrointestinal tract of the oral preparations.

Although it may eventually be possible to standardize the pure glycosides of digitalis by weight, assays of digitalis preparations are now required to be made by biologic tests. Formerly the frog method was official, a frog unit being defined as the amount of digitalis per gram of frog weight, which when injected into the ventral lymph sac of male frogs (20 to 30 gm.) produced permanent systolic standstill in one hour at room temperature. The cat method is now used. The amount of dissolved drug, injected intravenously, necessary to cause cessation of the cat's heart beat is compared with the amount of the standard necessary to produce this lethal effect. At least six cats each are used for the standard preparation and for that which is being assayed, and specific conditions relating to the size and character of the animals, to the character and depth of anesthesia, and to the method of injection, are set forth. The potency of the assayed preparation is expressed in U.S.P. units per cc. obtained by dividing the average lethal dose in cc. of the standard preparation by the average lethal dose in cc. of the assayed material.

This method of assay is far from ideal and does not accurately and consistently measure the effect of the drug as given to humans, by mouth and in therapeutic doses, as contrasted with its assay in animals, given intravenously and in lethal doses. Gold[71] showed that a variety of digitalis preparations of identical potency in cat units exhibited a ten-fold range of activity in humans. Assay in humans by electrocardiographic modification has been attempted but is still unsatisfactory.[67] Chemical and colorimetric assays have likewise failed to yield consistent results or reliable measurements of therapeutic activity in humans.[34]

The Administration of Digitalis

Modern concepts of adequate digitalis dosage are based on the detailed studies of Eggleston[47] with standardized digitalis preparations. For a long time inadequate doses were utilized with unsatisfactory effects despite Withering's[183] admonition that the drug "be continued until it acts either on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects." On the other hand, it is usually possible to obtain a satisfactory therapeutic effect without quite causing the symptoms mentioned by Withering, for these symptoms are evidences of overdosage. *The fundamental principle of digitalization is to administer the drug until the desired therapeutic effect is achieved or toxic symptoms appear.*

The technic of administering digitalis includes: (1) the induction of digitalization rapidly or slowly until the desired therapeutic effect is obtained without

symptoms of overdosage; and (2) subsequent maintenance of digitalization so that the benefits of the drug are retained continuously as long as necessary.

1. Methods of Inducing Digitalization (Oral Methods). While the total dosage necessary to obtain a maximum therapeutic effect without toxic symptoms varies from patient to patient and even in the same patient at different times, Eggleston[47] has shown that this dose can be predicted approximately from the weight of the patient. Allowance must be made for the amount of digitalis eliminated or destroyed by the body during the period in which digitalization is induced. Therefore a larger total dosage is required to digitalize a patient in one or two weeks than to digitalize him in one or two days.

In practice, we have learned the approximate oral digitalizing dose for the various digitalis preparations and this amount is given in single or divided amounts within the period to be allowed for digitalization.

The average digitalizing doses (within twenty-four hours or less) for the commonly employed digitalis preparations are:

	Average	*Usual Range*
Digitalis leaf	1.2 gm.	1.0 to 1.5 gm.
Tincture of digitalis	12.0 cc.	10 to 15 cc.
Digitoxin	1.2 mg.	1.0 to 1.8 mg.
Digoxin	3.75 mg.	2.5 to 5.0 mg.
Lanatoside C	7.5 mg.	5 to 10 mg.

Very large persons may require more, and small or aged persons somewhat less. Larger doses of digitalis than the above-stated average may be necessary to attain a satisfactory therapeutic effect in patients with very severe congestive heart failure, and when failure is associated with active rheumatic fever, infections or hyperthyroidism. Children above the age of four have been found by McCulloch and Rupe[121] to require considerably more digitalis per body weight than the doses given above for adults. Sutton and Wyckoff,[169] however, found no essential difference in their study on the treatment of children with rheumatic heart disease.

The important point to remember is that the above doses are practical average figures which may require considerable modification in individual cases. Much larger doses may have to be administered if a satisfactory therapeutic effect is not obtained or the drug may have to be stopped before the full estimated dose is given if more than mild symptoms of digitalis intoxication appear. Two weeks are usually required for the elimination of digitalis from the body. If digitalis has been administered in the preceding two weeks and further digitalization appears necessary, the amount remaining may possibly be calculated and subtracted from the dose that would have been given if the patient were digitalis-free. But if there is any doubt it is safer to digitalize slowly by administering digitalis leaf powder 0.1 gm. every six hours and observe the patient carefully for therapeutic or toxic effects. Because of their speedier elimination lanatoside C (Cedilanid), 1 mg. three times a day, or digoxin, 0.5 mg. three times a day, may be preferable in these circumstances. Because relatively large amounts of digitalis are contained within the intercellular and other body fluids of edematous patients, active diuresis with mercurial diuretics may transport this stored digitalis into the blood stream with redigitalization of the patient. This phenomenon, which may induce digitalis toxicity, should be considered in determining dosage.

The speed with which digitalization is induced depends on the urgency of

the patient's clinical condition. The following oral methods have been found practical, but they may be modified.

Rapid Digitalization in One Day or Less. This method applies to patients with acute congestive heart failure, especially when caused by a paroxysm of auricular fibrillation with extremely rapid ventricular rate, and to patients with severe chronic congestive heart failure. When digitalization is required within four hours or less, intravenous therapy should be employed (p. 187). However, Evans et al.[53] have found 2 to 3 mg. of digoxin, given orally, satisfactory for digitalization in four hours. Rapid oral digitalization may also be effected by digitoxin. A single dose of 1.2 mg. usually effects digitalization in six hours. The following table represents the usual initial and subsequent doses for rapid digitalization (24 hours) with various digitalis preparations:

	Initial dose	*Dose every 6 hours thereafter until digitalization*
Digitoxin	0.6 mg.	0.2 mg.
Digitalis leaf	0.6 gm.	0.2 gm.
Digoxin	1.5 mg.	0.5 mg.
Lanatoside C	3.0 mg.	1.0 mg.
Tincture of digitalis	6.0 cc.	2.0 cc.

Digitalization in Three Days. This method is useful for patients with well-developed but not urgent signs of congestive heart failure. Digitalization can be accomplished fairly rapidly at the same time that toxicity is more readily avoided because it is easier to stop short of excessive dosage. A dose of 0.2 gm. of powdered digitalis leaf (or 0.2 mg. digitoxin or 0.5 mg. digoxin) is given three times daily for two or three days. If the rapidly excreted digoxin or lanatoside C is used, it is preferable to give the total daily dose in the morning, instead of dividing it into three doses per day. Thereafter dosage is determined by therapeutic effect or the development of toxicity.

Slow Digitalization in One Week. This method is practical for mild or moderately decompensated patients, for ambulant patients examined only in the office or hospital outpatient department who are not likely to be seen oftener than once a week, and for patients with uncertain amounts of unexcreted digitalis. Either 0.1 gm. of powdered leaf or 1 cc. of the tincture is given three times daily, or 0.3 mg. digitoxin or 0.75 mg. of digoxin or 1.5 mg. of lanatoside C is given in a single daily dose until the desired therapeutic effect is achieved or toxic manifestations supervene. Many patients will require continuation or elevation of this dosage, as determined by the clinical status at the end of a week. In other cases the dosage may be reduced to the level necessary for maintenance.

Criteria of Therapeutic Effect. Having carried out one of the above schedules of dosage the physician must determine whether satisfactory digitalization has actually been attained, i. e., whether the patient has had a maximum therapeutic response. If not, and regardless of the dosage already administered, the recommended dose of digitalis should be continued until adequate benefit is secured or toxic symptoms appear.

In patients with auricular fibrillation and a rapid ventricular rate, slowing of the heart and elimination of a pulse deficit are approximate criteria of favorable digitalis effects. As a rule the heart rate is slowed to 70 to 80 per minute, but some patients are comfortable only if the resting cardiac rate is slowed to about 60, for it may rise considerably with slight activity. On the other hand,

it is not safe to continue digitalis until such slowing is obtained without regard to other manifestations, for digitalis intoxication may occur while the heart rate is still relatively rapid. However, even slower rates may be safely achieved if there are no toxic signs or symptoms. Furthermore, a rapid pulse rate may be misleading when due to ventricular extrasystoles resulting from digitalis intoxication. For the rapid rate may be interpreted as indicating that the patient's condition is worse and that he is in need of larger doses of digitalis. Therefore, the cardiac and pulse rate are guides to the administration of digitalis only when considered in connection with the patient's clinical course as regards both the symptoms of heart failure and those of digitalis overdosage (p. 189).

In patients with regular rhythm, a satisfactory therapeutic effect of digitalis is indicated by relief of dyspnea, orthopnea or cardiac asthma, by diuresis and loss of edema, disappearance of râles at the bases of the lungs and a diminution in the venous pressure and circulation time. Unless evidences of digitalis intoxication appear, the drug should be continued as directed until the above benefits are obtained.

2. Maintenance of Digitalization. When the optimal response has been obtained, it is important to maintain a continued state of therapeutic digitalis saturation by administering smaller doses of medicament to compensate for the amount excreted or destroyed by the body. According to Gold and DeGraff,[73] the patient does not excrete a fixed amount of drug each day but a fraction of the amount present in the body. Thus 0.2 gm. of digitalis may be excreted daily and may have to be administered daily to maintain digitalization, after the patient has been digitalized with 1.5 gm. of digitalis leaf. However, if the patient has received no digitalis previously, a daily dose of 0.2 gm. may be cumulative and eventually effects digitalization.

In practice, the daily maintenance doses for the common digitalis preparations are:

Digitalis leaf	0.1 gm. (0.05 to 0.15 gm.)
Tincture of digitalis	1.0 cc. (0.5 to 1.5 cc.)
Digitoxin	0.15 mg. (0.05 to 0.2 mg.)
Digoxin	0.5 mg. (0.5 to 1.0 mg.)
Lanatoside C	1.0 mg. (1.0 mg. to 1.5 mg.)

As with the initial digitalizing dose, the maintenance dose must be adjusted to the individual and his clinical response. The above doses are approximations to be used as guides. It should be emphasized that most patients with congestive heart failure will require maintenance doses of digitalis for the balance of their life.

If symptoms of digitalis intoxication appear, either during the induction or maintenance of digitalization, the drug should be discontinued until the toxic symptoms disappear and for one to two days thereafter. Digitalis may then be resumed in smaller dosage. It should be recognized, however, that in patients with severe congestive heart failure the optimal therapeutic and the toxic dose are sometimes very close and that satisfactory results are obtainable only at the expense of mild symptoms of intoxication. In ambulant patients with mild congestive heart failure there is a wide margin between the therapeutic and toxic doses, and an optimal clinical result should be obtained with smaller doses and therefore without toxic symptoms.[73]

Digitalization of Children. Heart failure in children is usually due to rheumatic fever and rheumatic cardiovalvular disease, occasionally to congenital

heart disease. Persistent rheumatic activity with acute and subacute carditis is the rule in the rheumatic cases of heart failure and this prevents or obscures the therapeutic efficacy of digitalis. This is probably the reason for the frequent statement that children require 50 to 100 per cent more digitalis per pound of body weight than do adults.[121] Similarly pronounced arterial anoxemia in children with congenital heart disease and heart failure impairs the therapeutic action of digitalis. It is probable that the proper dosage for children, as compared with that of adults, is proportionate to their relative weights.

To avoid the toxic symptoms which occur with disproportionate frequency in digitalized children, very rapid digitalization should be shunned, and dosage should be gauged by therapeutic effect rather than by arbitrary calculation. For children weighing between 50 and 100 pounds, one-half the adult dose may be used as an approximate amount for initial digitalization; below 50 pounds one-sixth to one-quarter the adult dose should be given. Taussig[171] recommended digitalization by administering 0.1 gm. (1½ grains) of digitalis leaf three times daily until optimal therapeutic effect is obtained or toxic symptoms appear. She then advised a maintenance dose of 0.05 to 0.1 gm. (¾ to 1½ grains) daily, with complete omission of the drug for one or two days each week. Because the strength of digitalis has been increased since these doses were recommended, it is advisable to reduce the dose 20 to 25 per cent below these figures or to anticipate more rapid digitalization.

Intravenous Administration of Digitalis or Strophanthin (Ouabain). The intravenous administration of digitalis is indicated only in emergencies requiring digitalization within a few hours. This might be necessary for patients with acute congestive heart failure due to an attack of paroxysmal auricular fibrillation with very rapid ventricular rate, patients with acute congestive heart failure and massive pulmonary edema or undigitalized patients with chronic congestive heart failure who are moribund. As a rule, however, sufficiently rapid digitalization can be obtained by the oral route. Sometimes intravenous digitalization is employed when the patient cannot take oral medication because of vomiting or because of coma. Ouabain or digitalis preparations should not be given intravenously if the patient has received a digitalis preparation in the preceding two weeks. In general, the intravenous administration of digitalis or strophanthin is rarely essential.

When intravenous digitalization is necessary, ouabain, the crystallized glycoside from G strophanthus, is preferred to digitalis preparations because of its more rapid action (five to forty-five minutes as compared to two or three hours). Furthermore the effect of ouabain is dissipated more rapidly (one to two days as compared to one to three weeks for digitalis). There has been some fear of using strophanthin and ouabain which are powerful poisons (used long ago as arrow poisons) and which can produce premature beats, ventricular tachycardia or fibrillation and death within a half hour after injection. But it is doubtful whether the relation of therapeutic to toxic dose for ouabain is different from that of the digitalis glycosides. Most of the reported accidents may have been due to previous digitalization with incomplete elimination at the time ouabain was injected or to overdosage.

Wyckoff and Goldring[187] administered ouabain intravenously in patients with auricular fibrillation and rapid ventricular rate, with good therapeutic results and without dangerous incidents. The full therapeutic dose was found to be 1 mg. for 150 pounds of body weight. *A total dosage of 1 mg. of ouabain*

should not be exceeded in a twenty-four hour period. It should not be given at all if digitalis has been administered in the preceding two weeks. Wyckoff and Goldring[187] gave an initial dose of 0.5 mg. followed by injections of 0.1 mg. every half hour until a satisfactory therapeutic or toxic effect was obtained. A maximum action was usually observed in less than an hour. Slowing of the heart, thus obtained, persisted for five days or less. Another procedure is to give 0.25 to 0.5 mg. of ouabain intravenously in a single dose and simultaneously 0.6 mg. of digitoxin or 1.5 mg. of digoxin orally to continue digitalization, or digitalis leaf can be given in 0.2 gm. doses every six hours. According to this regime, the intravenous injection is utilized only for a speedy start but is not repeated.

Of the various digitalis preparations probably lanatoside C is the most desirable because it is a pure crystalline substance of constant composition and because it has the briefest latent period and the most rapid rate of elimination of the commonly available digitalis glycosides. Lanatoside C is marketed as Cedilanid in 2 cc. and 4 cc. ampules containing 0.2 mg. per cc. Sokolow and Chamberlain[160] used it in doses up to 14 cc. per day in 38 cases. In general 8 cc. was the digitalizing dose, and 6 to 14 cc. in twenty-four hours in divided doses digitalized most patients. In practice one may inject 4 cc. (0.8 mg.), repeat in four hours and thereafter give 2 cc. (0.4 mg.) every six hours as indicated. In cases of auricular fibrillation the ventricular rate sometimes falls to 40 or 50 within thirty minutes to two hours. Maintenance doses of digitalis should be continued orally if possible after digitalization has been effected.

Other commercial solutions of digitalis, provided in sterile ampules for intravenous injection, are available, for example, digalen, digifoline or digitan. According to Pardee,[136] a safe and satisfactory initial dosage is 6 to 8 cat units (0.45 to 0.60 gm.) administered slowly. If a satisfactory clinical result is not obtained within two or three hours, a second injection of 2 cat units (0.15 gm.) may be given, and repeated again if necessary in three hours. Slowing of the heart may occur within fifteen minutes but the maximum effect usually appears two to three hours after the injection and persists for twelve to twenty-four hours. Digitalis should not be given intravenously if the patient has received digitalis in the preceding two weeks. Often, after the initial dose, digitalis therapy can be continued orally in doses of 0.2 gm. every six hours until the desired effect is obtained. The above solutions have been administered in similar dosage intramuscularly or hypodermically when a vein cannot be entered and urgent digitalization is required.

Rectal Administration of Digitalis. Digitalis may be administered rectally to patients who cannot take oral medication because of nausea and vomiting due to the congestive heart failure or to other causes. According to the method advised by Levy,[108] the patient is given a cleansing enema followed by the total estimated dose (usually 8 to 20 cc.) in 30 to 60 cc. of saline. One of the above-mentioned aqueous solutions prepared for parenteral use is administered. The tincture should not be employed unless well diluted, because of the irritating effect of the alcohol. For slower digitalization (in two days) Willius[181] recommended 6 cc. of the standardized tincture dissolved in 100 cc. of normal saline once daily, or 2 to 2.5 cc. of the tincture in 60 cc. of saline, daily, to obtain a therapeutic effect in three to five days. In general the usual dose is increased 25 per cent when digitalis is given rectally. Rectal digitalization may also be effected by suppositories but these are rarely necessary or desirable.

Evidences of Digitalis Overdosage. Toxic manifestations are an essential feature of overdosage with any effective preparation of digitalis or of a drug with digitalis-like action. Claims that a given preparation of digitalis never produces such toxic symptoms are either untrue or indicate the inertness of the preparation concerned. Patients differ greatly in their tolerance to digitalis; consequently some present toxic symptoms with doses which are ordinarily considered inadequate therapeutically. In some patients, especially those with very severe congestive heart failure, the toxic and therapeutic doses are almost identical and it is difficult to obtain satisfactory clinical improvement without evoking mild and recurrent toxic symptoms.

The most common evidences of overdosage with digitalis are those representing (1) *gastrointestinal disturbances* and (2) *disturbances in cardiac rhythm.*

Anorexia, Nausea, Vomiting. Nausea and vomiting are the commonest early symptoms of digitalis overdosage. Usually these are preceded for a day or two by moderate or complete anorexia. When the latter is noted after an average therapeutic dose of digitalis, the more annoying vomiting may be prevented by prompt discontinuance of the drug. The vomiting is of central, not of gastric, origin for it appears even after intravenous injections of digitalis,[86] and in animals nausea and vomiting movements were induced by Hatcher and Eggleston[85] following the administration of digitalis even when the gastrointestinal tract had been removed. (However local gastric irritation can result from large initial dosage of whole leaf tablets.) Whether the vomiting results from direct stimulation of the vomiting center in the medulla or by a reflex from the heart is still a controversial question.

The chief practical problem presented by the appearance of nausea and vomiting during the administration of digitalis is to determine whether these symptoms are due to the drug, which would demand its discontinuance, or to uncontrolled congestive heart failure (p. 59), which would require continued or increased dosage. Unfortunately for such decisions some patients, as shown by Eggleston,[47] vomit after only one half to two thirds of the usual digitalizing dose while others require as much as 8.5 gm. before vomiting appears. If a beneficial therapeutic result has been obtained or if the dose administered is nearly equal to the amount estimated for digitalization, it is best to discontinue the drug for one to three days and then resume it in smaller doses. If less than two thirds of the estimated dose has been given when vomiting appears, if there are no other toxic symptoms (such as bigeminal rhythm), and if the symptoms of congestive heart failure are still uncontrolled, it is preferable to continue the digitalis despite nausea and vomiting, with careful observation for the possible development of other toxic manifestations of the drug. Nausea and vomiting in patients with congestive heart failure are often due not only to the congestive failure itself but also to psychic factors. These symptoms frequently subside if food, fluids and medication by mouth are eliminated for a brief period while sedatives are administered and digitalis is continued intravenously or rectally.

Diarrhea was noted by Withering[183] as a consequence of digitalis but this is uncommon except with very excessive doses. However, when this symptom appears during digitalis medication, the possibility that it represents intoxication with the drug must be considered. Other evidences of digitalis overdosage will be found if this is the case.

Cardiac Disturbances. PREMATURE BEATS AND BIGEMINI. Next to the gastrointestinal symptoms, premature beats (extrasystoles) are the commonest manifestations of digitalis overdosage. While these usually appear later than nausea and vomiting, sometimes they and other toxic digitalis symptoms appear in patients who do not vomit at all. Therefore the physician must watch for them and beware the sense of false security which may be engendered by the absence of nausea and vomiting.

A characteristic form of premature beats associated with digitalis overdosage is that termed *bigemini,* an arrhythmia in which every normal beat is followed by a premature contraction. Premature beats of various types including bigemini also occur in patients who have not received digitalis. When such patients are in heart failure, digitalis is not contraindicated and the medicament may actually eliminate the premature beats. When, however, bigemini first appear during digitalization, they must be interpreted as an evidence of overdosage and the digitalis should be interrupted for at least a day after they disappear. If the premature beats (isolated or in bigeminal rhythm), are due to digitalis, they are almost always of ventricular type, and vary in electrocardiographic configuration because they are of multifocal origin.[148b] Sometimes alternating left and right ventricular premature beats are seen with toxic doses of digitalis. In patients with auricular fibrillation, the presence of bigemini may still be recognizable by the coupling of the pulse produced during the periods of extrasystoles, but often electrocardiograms are necessary for their discovery in such cases. While extrasystoles in animals occur only after huge doses (50 to 75 per cent of the lethal dose), in man they may appear after only three or four doses of 0.1 gm. of the powdered leaf. Usually, however, they appear after an adequate therapeutic dosage.

DISTURBANCES IN CONDUCTION. *Excessive slowing of the pulse* is another evidence of digitalis overdosage. Usually the drug should be discontinued if the heart rate falls below 60 per min. and almost always if it falls below 50. Various grades of partial *heart block* up to complete heart block may occur. McGuire and Richards[122] reported the development of complete heart block in the normal heart of a person who took 30 gm. of digitalis with suicidal intent. In patients with congestive heart failure, digitalis often causes partial heart block due to impairment of atrioventricular conduction. But this may occur occasionally, even with therapeutic doses. If such dosage is not exceeded, digitalis may be administered to patients who already show partial heart block without increasing the delay in conduction.

DISTURBANCES IN SINUS RHYTHM AND SINOAURICULAR CONDUCTION. By its vagal action, toxic doses of digitalis may depress sinoauricular impulse formation or sinoauricular conduction. As a result digitalis may induce sinus arrhythmia, sinus arrest, sinoauricular block and auricular standstill. By a similar mechanism of sinus depression, digitalis intoxication may evoke auriculoventricular nodal rhythm, nodal rhythm with auriculoventricular dissociation, reciprocal and interference beats. These arrhythmias are discussed in Chapter 11.

AURICULAR FIBRILLATION AND TACHYCARDIAS. *Auricular fibrillation* is frequently induced by therapeutic doses of digitalis in patients with auricular flutter (p. 271). However, this and, rarely, auricular flutter may develop in hearts with normal rhythm after toxic doses of digitalis.[144] *Tachycardia* as well as excessive slowing of the heart may represent digitalis intoxication. This may be due to numerous ventricular extrasystoles which result only from excessive digitalis. If the toxic significance of the tachycardia is unrecognized and digitalis

therapy continued, *paroxysmal ventricular tachycardia* may result.[143] Ventricular fibrillation may be a possible consequence of overdigitalization and may account for cases of sudden death due to intravenous strophanthin. In humans who were subject to attacks of ventricular fibrillation, Schwartz and Jezer[156] were able to precipitate such paroxysms with digitalis.

Other arrhythmias have also been occasionally evoked by toxic doses of digitalis. These include electrical and pulsus alternans and paroxysmal auricular tachycardia with or without 2:1 block.[90] The latter was induced repeatedly even with small doses of digitalis.

Nervous and Other Symptoms. Headache is relatively common with excessive digitalization. Occasionally visual blurring, scotomata, or colored vision (green and yellow) is produced.[146] Weakness and mental disturbances are not uncommon, especially in elderly patients. Despite the criteria set down by Carr[22] for attributing mental or psychotic disturbances to digitalis overdosage, it is often difficult to distinguish such a relationship, for the symptoms in cases which I have observed could also be attributed to rapid or excessive dehydration caused by restriction of fluid and salts, and especially to the diuresis produced by mercurial salts.[178] I have observed similar symptoms following excessive diuresis in patients with heart failure who have received no digitalis. Batterman and Gutner[7] described unusual neurologic manifestations of digitalis toxicity in 10 patients, characterized particularly by neuralgia of the lower third of the face, mandible or maxilla and by pain in the upper extremities, lower lumbar and calf muscles.

Other Toxic Effects. Eosinophilia, attributed to marked vagotonia caused by digitalis, has been noted by several observers.[147] Allergic disturbances have been described.[28] Dangerous and sometimes fatal results have been reported as resulting from the combined or successive administration of digitalis and other drugs, especially ephedrine[95] and calcium.[16, 158] When dealing with patients with heart failure, however, one must be cautious in attributing sudden death to an extraneous factor.

Thrombotic Effect of Digitalis. There have been claims that digitalis increases the coagulability of the blood,[113, 43, 119] but this has been disputed.[159, 145] The importance of this question lies in the purported tendency of digitalis to promote fatal embolization. This danger has been particularly emphasized in cases of acute myocardial infarction in which digitalis has been employed (p. 493).

Pathologic Myocardial Lesions. After large toxic doses of digitalis given to animals, microscopic examination reveals areas of focal necrosis, vacuolization or dissolution of muscle fibers, hemorrhages, cellular infiltration and fibrosis.[20, 36] Kyser and his associates[103] called attention to the similarity of these anatomic abnormalities to those caused in dogs by vagal stimulation or injections of acetylcholine. These similarities and their own experimental observations led them to conclude that the cardiotoxic effect of digitalis in the dog is due to vagal stimulation which causes coronary vasoconstriction. Atropinization or drugs causing coronary vasodilatation (aminophylline, theobromine) diminished the lesions produced by digitalis.

The Effect of Digitalis on the Electrocardiogram

It is extremely important to be familiar with the electrocardiographic changes caused by digitalis because some are characteristic of the drug and others may be indistinguishable from the changes caused by myocardial disease, especially

that due to coronary arteriosclerosis and occlusion. Digitalis has been employed by persons with normal hearts in order to mislead their physicians into making a diagnosis of myocardial disease with the aim of illicitly collecting disability insurance. The electrocardiogram is useful in discovering or confirming the presence of cardiac changes due to digitalis overdosage.

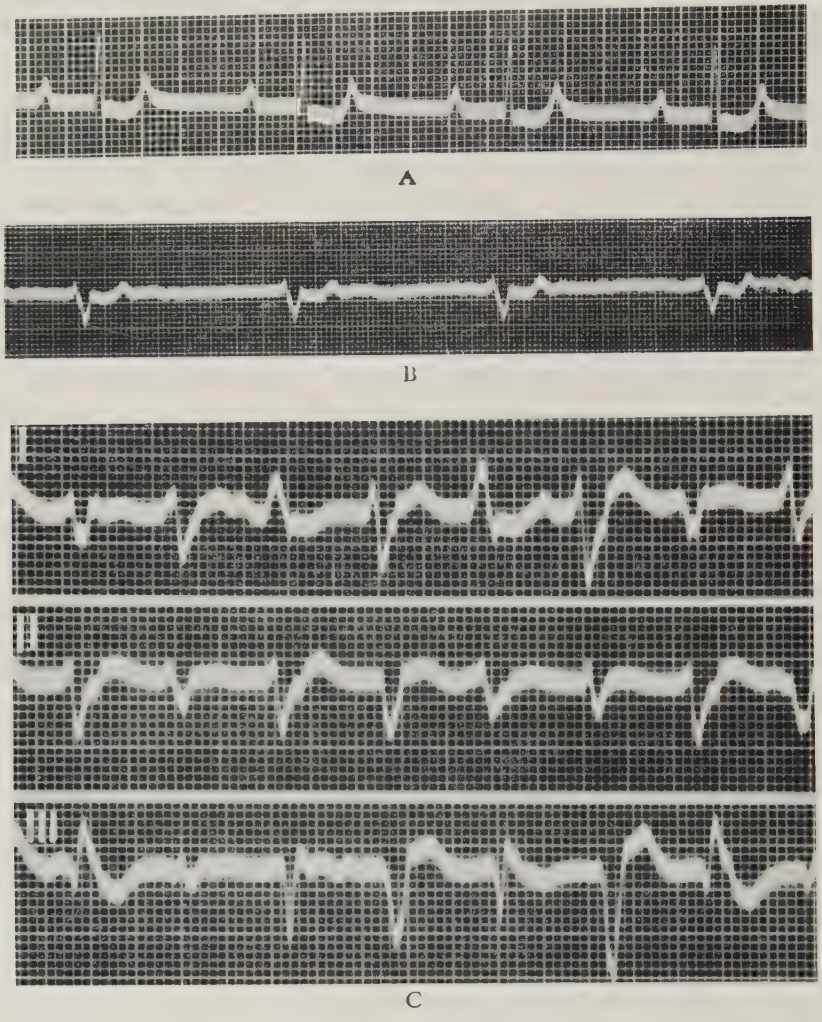


Fig. 23. Digitalis intoxication.

A, Prolonged P-R interval and S-T depression. Lead II.
B, Atrioventricular dissociation. Idioventricular pacemaker with regular rhythm despite atrial fibrillation. Lead II.
C, Ventricular tachycardia of multifocal origin.

The earliest and most important electrocardiographic effects of digitalis are on the RS-T interval and T wave (Fig. 23A). These occur in persons with normal as well as diseased hearts. They occur before full therapeutic benefits are obtained and therefore are no indication for discontinuing the digitalis.

A depression of the RS-T interval followed by an inversion of the T waves is

the characteristic change of digitalis[29, 19, 125] (Fig. 23A). The exact changes encountered differ somewhat in normal hearts and in those which showed electrocardiographic alterations before digitalis was begun. In *normal hearts* the chief effect is on the RS-T interval, the changes in the T wave being secondary to the displacement of the origin of the RS-T interval. The ST level first becomes depressed so that it begins below the isoelectric line and forms a curve which is concave upward. Later the S-T interval, starting below the isoelectric line, turns sharply downward and then forms a right angle as it turns up again to join the T wave. Finally the upward (second) limb of the ST segment turns up more sharply so as to form an acute angle. There is no true inversion of the T wave since its peak is still above the isoelectric line, but the changes in the S-T interval make the T wave appear either inverted or diphasic. Another characteristic is the slow downward slope from the peak of the T wave so that it hardly reaches the baseline when it joins the next P wave. These changes in the S-T interval and T wave are characteristic of digitalis and should not be mistaken for the T waves caused by myocardial disease.

In *diseased hearts* whose T waves were originally upright, the ST changes with digitalis are often indistinguishable from those in normal hearts. Frequently, however, digitalis produces alterations in such hearts which are indistinguishable from those due to myocardial damage secondary to coronary artery disease. There is a distinct ST segment depression, which may be convex upward, and a pronounced inversion of the T wave.

If, however, the T waves are inverted in all leads before digitalization, they usually become less inverted after digitalization, or the S-T interval may become depressed with significant change in the T waves. On the other hand if there is only slight inversion of the T waves before digitalis, the drug may increase the negativity of these waves. Occasionally negative T waves are rendered upright by digitalis. In cases with left axis deviation with upright T waves, the S-T interval in lead I may become depressed and T_1 inverted while ST_3 becomes elevated and T_3 upright, thus resembling the changes seen in anterior myocardial infarction.

In the precordial lead, Strauss and Katz[166] observed a depression or elevation of the S-T interval and diminution in the size of the T wave. Rarely the T wave disappeared or became inverted. RS-T segment deviations and T wave abnormalities in the precordial leads may simulate those due to coronary occlusion with myocardial infarction.[164]

Certain diagnostic conclusions can be drawn from the ST and T changes in the electrocardiograms of patients receiving digitalis. If they are the changes mentioned as being characteristic of digitalis, the patient may have a normal or a diseased heart. But if distinctly inverted T waves appear during digitalization, it is extremely likely that the heart is diseased, for the normal heart develops only the ST changes described as characteristic of digitalis. Since the ST and T changes, which may appear within two to four hours of a large therapeutic dose, do not disappear for two to three weeks, it is necessary for proper interpretation of the electrocardiogram to determine whether the patient has received digitalis in the preceding three weeks.

Other electrocardiographic changes appear later and usually only after excessive doses of digitalis. They are the graphic representation of the disturbances in rhythm and conduction enumerated above as the cardiac symptoms of digitalis overdosage (p. 189). These include premature beats, especially

bigemini, excessive slowing of the heart rate, prolongation of the P-R interval (Fig. 23, *A*), partial or complete heart block with dropped ventricular beats or atrioventricular dissociation (Fig. 23, *B*), auricular fibrillation, ventricular paroxysmal tachycardia (Fig. 23, *C*) and inversion, flattening or notching of the P wave, especially in lead III. The P wave changes can usually be eliminated by atropine. The duration of electrical systole, i. e., the Q-T interval, is shortened in comparison with the duration of the entire cardiac cycle R-R.[10] According to ter Horst,[172] the *absolute* value of the Q-T interval may be shortened, lengthened or remain unchanged depending on whether it was originally prolonged, of normal length or of less than normal length.

DIURETICS

In cases of relatively mild congestive heart failure, rest and limitation of salt often result in a satisfactory diuresis with concomitant clinical improvement. In others, such an effect is obtained only if digitalis therapy is also employed. But many patients with more severe symptoms of congestive heart failure, especially with widespread anasarca, respond satisfactorily only if diuretics are utilized in addition to the above measures. The fewer the measures required to obtain a good therapeutic result, the better in general is the prognosis. A variety of diuretics have had their vogue from time to time but the utility of any one of these has been dwarfed in recent years by the striking success of some of the soluble organic mercury salts. Since the mercurial diuretics have been used, many patients whose outlook for life would not average more than six months to a year have been maintained with various degrees of comfort for many years. Furthermore, certain of the fatal complications, such as pneumonia, occur less frequently than formerly since mercurials have been employed for successful diuresis with consequent diminution of pulmonary congestion and edema.[142]

Mercurial Diuretics

Calomel, formerly widely employed as a diuretic, often in combination with equal parts of digitalis and squill (1 grain each) as the famous Guy's pill, is now rarely used in treating cardiac dropsy because of its limited effectiveness and its toxicity. *Merbaphen* (novasurol), originally used in the treatment of syphilis, is an effective diuretic but is rarely used at present because of toxic complications. Colitis, stomatitis, purpura, hemoglobinuria, hemorrhagic encephalitis and epithelial necrosis of the kidney, sometimes with fatal results, have been reported. These complications are relatively rare with the more recently employed mercurials, *salyrgan* (mersalyl), *mercupurin* (novurit) and *mercuhydrin.* The mercurial diuretics now in use contain about 5 per cent of theophylline which may add somewhat to the diuretic effect, facilitates absorption of the mercurial component and probably reduces local irritation.[88, 38]

Action of Mercurial Diuretics. The mechanism by which the mercurial salts produce diuresis is uncertain. According to the studies of Herrmann and his co-workers,[89] the mercurials cause diuresis by liberating ionic mercury which inhibits tubular reabsorption. Sollmann and associates[161] found evidence to indicate that they may have an extrarenal action by which they mobilize water and salt from the tissues into the blood stream. Gibson and Evans[68] found that in edematous dogs diuresis was accompanied by a sharp decrease in blood volume and therefore suggested that fluid was extracted from the engorged

capillaries in the various tissues and organs. A similar fall in blood volume occurs after diuresis and symptomatic improvement in clinical cases of congestive heart failure. However the extrarenal theory of mercurial diuresis has been generally rejected.

It is most probable that the mercurial diuretics act directly on the kidneys,[80, 175] decreasing the reabsorption of sodium and water by the proximal tubules.[13] There is no change in renal blood flow or glomerular filtration. The ingenious experiments of Duggan and Pitts[45a] suggested to them that the mercurial acted on the distal tubule, but their data could be equally interpreted to support an action on the proximal tubule. When mercurial anuria is produced, the pathologic lesions are in the proximal tubule. The predominant effect of the mercurial diuretic is on the excretion of sodium.[62] The pronounced diminution of sodium excretion by the kidney, which is characteristic of congestive heart failure, is reversed by mercurial diuretics. Following intravenous injection, diuresis begins within one to two hours after administration of the mercurial, reaches its peak in four hours and is usually completed in twelve to twenty-four hours. A daily excretion of 2 to 3 liters is commonplace after a mercurial diuretic and concomitantly there is a weight loss of 2 to 5 pounds. Occasionally, huge amounts of urine are excreted. Careful attention to the weight is a useful method of gauging the effectiveness of the diuretic.

Sometimes patients in heart failure become unresponsive to mercurial diuretics ("mercury fastness"). Usually this is observed in the end stages of failure and after numerous injections of mercurials. This unresponsiveness has been attributed to low glomerular filtration and the consequent small amount of sodium reaching the tubules. Thus this small quantity of sodium can be completely or almost completely reabsorbed despite the action of the mercurial. The administration of sodium may permit a mercurial diuresis, but more sodium will be retained than is excreted. It is probable that in the so-called state of mercury fastness more fundamental processes associated with advanced heart failure are responsible for the unyielding sodium and water retention.

Indications for Mercurial Diuretics. The mercurial diuretics are indicated in all stages of congestive heart failure but especially when the symptoms fail to respond to rest, digitalis and the limitation of sodium salts. The most striking benefits are seen in patients with intense anasarca, but a sharp diuresis and loss of weight are frequently observed in patients with latent edema. Furthermore, remarkable benefit may be obtained from the mercurial diuretics in cases of congestive heart failure (pulmonary congestion with or without pulmonary edema) in which failure is limited to the left side of the heart. Patients with orthopnea, nocturnal dyspnea (cardiac asthma), nocturnal cough due to heart failure or with recurrent attacks of pulmonary edema may be greatly relieved by the administration of the organic mercurials. Mercurial dehydration may be indicated as a prophylactic measure against recurrent paroxysmal dyspnea. In such patients Alsever and Levine[2] found that there was an average increase of 290 cc. in the vital capacity of the lungs in twenty-four hours after a mercurial diuretic, with concomitant improvement in subjective respiratory distress and diminution in the signs of pulmonary congestion. The administration of mercurial diuretics often serves as a therapeutic test in determining the cardiac or noncardiac origin of protracted cough or dyspnea of uncertain origin.

The mercurial diuretics are equally effective in cases of congestive heart

failure with auricular fibrillation or with regular rhythm. But, compared to digitalis effects, their action is much more impressive in the latter group in which digitalis often fails to produce a significant diuresis. Frequently the mercurial diuretic will evoke a sharp diuresis and loss of edema after rest and digitalization have been given a fair trial without much benefit. Less often, this is observed in digitalized cases of auricular fibrillation with extensive subcutaneous edema. Cases of congestive heart failure due to coronary arteriosclerosis, hypertension or rheumatic heart disease respond to the mercurial diuretics with equal effectiveness. Apparent differences of response in certain series of cases are probably due to other factors than the etiologic disease. Cases due to syphilis, those in which heart failure is secondary to pulmonary disease and those due to mechanical impediments such as constrictive pericarditis do not respond nearly as well to mercurial diuretics or to any other form of medical therapy.

Contraindications to Mercurial Diuretics. The chief contraindication to mercurial diuretics is renal impairment. But albuminuria or nitrogen retention in the blood does not necessarily forbid the use of these drugs because heart failure itself may produce these abnormalities. That they are actually due to heart failure and not to renal insufficiency may be recognized by the dark color of the urine with its richly colored sediment and by the high specific gravity of the urine (1.020 or more) as obtained in a casual specimen or after a concentration test. On the other hand if the urine is pale and the specific gravity is 1.014 or less in patients with heart failure, it is probable that there is renal insufficiency and mercurials should not be administered. This rule is not applicable if the urine is examined when the patient is in the process of active diuresis.

The mercurial diuretics are contraindicated when heart failure is associated with acute or subacute glomerulonephritis, as they may increase the hematuria or cause anuria. I have seen both temporary and fatal anuria caused in such cases by the use of salyrgan or mercupurin. However, further study of the possible usefulness of mercurial diuretics in renal edema is needed. The mercurial diuretics should be used with caution and in relatively small doses in elderly patients who are likely to have urologic diseases. Tscherning[174] has reported the occurrence of acute retention in old men with large prostate glands, which was attributed to a profuse salyrgan diuresis. Hines[93] reported a high incidence of uremia in a series of patients with hypertensive and arteriosclerotic heart disease and congestive heart failure.

Mercurial diuretics irritate the colon and are therefore contraindicated in the presence of *inflammatory lesions of the large bowel.* For the same reason it is advisable not to administer purgatives acting on the colon on days when salyrgan or mercupurin is administered.

Toxic and Other Undesirable Effects of Mercurial Diuretics. The toxic and undesirable effects of mercurial diuretics may be considered under five headings:

1. Excessive sodium loss and dehydration
2. Immediate reactions
3. Mercurialism
4. Local irritation
5. Redigitalization

1. Excessive Sodium Loss and Dehydration. Excessive and too rapid diuresis by mercurial diuretics is often accompanied by moderate or extreme states of weakness and dehydration.[161a] Muscular fatigue or severe muscle cramps

may result from sudden losses of sodium. Weakness is common following frequently repeated diuresis, and prostration or collapse occurs occasionally. Disproportionate loss of sodium as compared to water may produce a clinical picture resembling water intoxication. On the other hand, azotemia sometimes follows profuse diuresis without a proportional excretion of nitrogenous waste products.[62] Fixation of specific gravity of the urine at 1.010 may persist for several weeks after vigorous desalting with mercurials. Pronounced hypochloremia and alkalosis may also occur. Cerebral thrombosis and hemiplegia have been attributed to profound diuresis and fall in blood pressure engendered by the injection of mercurial diuretics in full therapeutic doses.[148a]

Psychotic disturbances (delirium, drowsiness, mental confusion), often attributed to digitalis overdosage, may also be due to overenthusiastic dehydration. Some of the cases of so-called cardiac cachexia may be due, in part at least, to excessive diuretics. Poll and Stern[139] reported 7 such cases with 3 deaths due to rigid mercurial diuresis. After a period of preliminary weakness, intense anorexia and mental apathy, the patients suffered from restlessness, mental confusion and rarely hallucinations and delirium. Progressive coma and death ensued in some cases. The patients had experienced intense thirst, and it is probable that they suffered from severe dehydration. These manifestations of sodium and water loss may be alleviated by temporary cessation of diuretic therapy and by an increased allowance of sodium and fluid intake.

Occasionally profuse diuresis may lead to a sufficient loss of calcium to produce tetany in predisposed individuals.[135, 116] Other metabolic disturbances associated with intense diuresis may account for the instances in which an attack of gout was precipitated in gouty individuals.[140]

2. Immediate Reactions. A number of serious and even fatal reactions have been reported immediately after injection of mercurial diuretics, even in patients who had had many previous injections of the same drug.[179] Chills, fever,[125a] nausea and vomiting and cutaneous rash, occurring on the day of injection, have been attributed to drug idiosyncrasy. Among the immediate reactions to the injection of mercurial diuretics are transient dizziness, weakness, substernal oppression, dyspnea or asthmatic attacks, and changes in cardiac rhythm. They occur very rarely. In some instances collapse and sudden death have followed an injection of a mercurial diuretic.[98] The cause of these reactions is uncertain.[179] Ben-Asher[8] believed that he prevented a recurrence of reaction by injecting the mercurial very slowly or giving it after an intravenous infusion of sodium thiosulfate, or by injecting it intramuscularly. Sometimes a change to another mercurial eliminates further untoward reactions. In these circumstances sensitivity is not related to the mercury ion but to the given organic compound.

3. Mercurialism. Manifestations of mercurial poisoning are relatively rare with the organic mercurial preparations now in use.[40] Stomatitis with excessive salivation, dermatitis, colitis with diarrhea which may be hemorrhagic, and renal disturbances (hematuria, anuria and renal insufficiency) have been reported on occasion.

4. Local irritation is an annoying characteristic of the mercurial diuretics, but mercuhydrin appears to be relatively free from this effect. Intramuscular injection may be moderately painful, even when properly performed, and it may be extremely irritating if the drug infiltrates the subcutaneous tissues. Imperfect intravenous injections cause a severe periphlebitis with pain and disability lasting several days, and occasionally followed by tissue necrosis. It

is essential that the needle be properly placed within a vein before the drug is injected and repeated aspiration of blood should be performed to be certain the needle has not slipped.

5. Redigitalization. Another reported complication of rapid diuresis with mercurials is the mobilization of digitals from edema fluid and serous effusions.[153] During digitalization some of the digitalis is retained in the body fluids. In the course of active diuresis the digitalis-containing extracellular fluid has been presumed to reenter the bloodstream and to cause redigitalization or excessive digitalization of the patient, with consequent ventricular slowing, arrhythmias, vomiting and mental confusion.

According to Macht[114] injection of mercurial diuretics reduced the clotting time of the blood of rabbits and cats. It remains to be seen whether these reported experimental observations of the thromboplastic effect of mercurial diuretics are of clinical significance in humans.

Despite the occasional toxic effects of salyrgan and mercupurin, these drugs are rarely dangerous if used with discretion and with regard to the above contraindications. There are many patients now who have received many hundreds of injections of mercurial diuretic without apparent harm. Fineberg[56] has reported a case in which 343 injections of salyrgan and mercupurin were given without deleterious effect over a period of seven and one-half years. Friedenson[63] reported a similar case in which 627 injections were administered over a period of twelve years. In the past five years I have given one patient with heart failure due to rheumatic heart disease more than 700 intravenous injections of mercurial diuretics. Tarr and Jacobson,[170] in a study of 30 necropsies on subjects who had received salyrgan for a long time, found indications of renal damage caused by the mercurial in only one case.

The Administration and Dosage of Mercurial Diuretics. The soluble organic mercurial diuretics may be administered intravenously, intramuscularly, orally, by rectal suppositories or intraperitoneally. At least one mercurial may also be given subcutaneously (infra). Mercuhydrin, mercuzanthin (mercurophylline) and salyrgan-theophylline are those in common use. They are equally effective as diuretics but it appears that mercuhydrin is unlikely to cause local irritation after intramuscular injection. The mercurials should be administered in the morning, if possible, in order that most of the diuresis is completed before the patient retires for the night.

Usually I begin with an intramuscular (gluteal) injection of 0.5 cc. (8 minims) to test the patient's sensitivity. If this causes headache, fever, gastric disturbances or a rash, I change to another mercurial which may be better tolerated. If there are no untoward symptoms after this preliminary injection and no significant diuresis results, I administer 1 cc. (15 minims) of the medicament in twenty-four to forty-eight hours, depending on the urgency of the case. This dose is usually adequate for continued diuretic action and should be repeated according to need. Two cubic centimeter doses produce a more profuse diuresis and may be preferable but the increase in urinary output is less per cc. of the drug.[131] On rare occasions 3 to 4 cc. doses may be effective when the smaller doses have failed. In general I have preferred intravenous injections after the first test doses. The importance of careful intravenous injections and avoidance of infiltrating the perivenous tissue has been noted. All intravenous injections must be given *slowly*.

If intravenous injections are difficult to perform or undesirable, repeated

doses of the mercurials may be administered *intramuscularly,* except as noted below. A nonedematous area should be chosen so as to permit absorption. Usually the injection is given in the upper and outer quadrant of the buttock. When the patient is obese, the needle should be of sufficient length to reach the muscular tissue. Sometimes the injections cause painful, nodular infiltrations. For this reason it may be desirable to add 1 cc. of 1 per cent novocain to the mercurial solution before injecting it into the muscle. If intramuscular injections are ineffective, it is always wise to switch to the intravenous route. Following such a change in procedure, I have several times observed an effective diuresis after the intramuscular injection had been impotent.

Recently thiomerin, containing a sulfhydryl (mercapto) group but no xanthine, has been found as effective as the above-mentioned mercurials and virtually without systemic reaction or unusual local discomfort when given by subcutaneous injection.[81a, 88a] This is an important advance, as it is possible to teach cardiac patients to give their own injections as diabetic patients administer insulin. Mercuhydrin has recently also been reported to be safe and effective when given subcutaneously.[167a]

Frequency of Injections. The frequency of mercurial injections depends on the clinical course and the patient's response. A thorough elimination of all edema fluid, obvious and latent, in the pulmonary as well as systemic tissues, is the desired objective. A daily record of the patient's weight, carefully determined, is the most useful guide to control of his retention of fluid.[78] A record of intake and output of fluids may also be useful but only if these are carefully observed. Gold[71] recommends the administration of a daily mercurial diuretic in combination with other therapeutic measures until the patient's "dry" or basal weight is obtained. (This is rarely necessary and may be hazardous.) Thereafter the injections are spaced at intervals which will prevent fluid retention. Obviously, the more rigid the limitation of sodium intake, the less often or the less likely the need for the diuretic. In practice, mercurial diuretics are administered between twice weekly and once in two weeks. However, the frequency of injections should be individualized for each patient as determined by symptomatology and clinical examination as well as weight. It is rarely desirable to cause daily weight losses exceeding 2 to 3 pounds, if symptoms of dehydration and prostration are to be avoided.

Oral administration of mercurial diuretics produces a satisfactory response in many patients with congestive heart failure.[15] When effective, oral mercurial diuretics possess the advantages of continuous instead of intermittent diuresis, avoidance of injections or of diminishing the frequency of the latter. They may be more practical in ambulatory patients who do not visit a physician frequently. However, adequate supervision by a physician is required because of the occasional occurrence of mercurialism or other toxic manifestations. Abdominal cramps, with or without diarrhea, nausea, painful gums or albuminuria, were the common symptoms noted by Derow and Wolff.[42]

The oral preparations of salyrgan-theophylline, mercuzanthin and mercuhydrin are tablets containing about 30 mg. of mercury or slightly less than 1 cc. of the parenteral preparation. Various dosage schedules have been employed such as two or three tablets each morning after breakfast, one tablet three times daily, or five tablets in a single dose every few days. Individualization of dosage is essential for satisfactory results.

Intraperitoneal injections in the same doses are sometimes made in patients

with severe congestive failure and ascites when intravenous administration has not been effective. In such cases Meyer and Freundlich[128] reported excellent results. But severe reactions may occur. I have found no need nor advantage in peritoneal injections.

Suppositories of mercupurin (mercurin) and other mercurials have been developed for *rectal administration.* They contain 0.5 gm. of the mercurial, or 200 mg. of mercury, i.e., two and a half times as much mercury as in the 2 cc. ampule. They may be as effective as when the drug is given parenterally and avoid the need for injections.[41, 64] But this advantage is more readily obtained by the use of oral mercurial diuretics. The suppository should be inserted, if possible, after a cleansing enema. Occasionally rectal irritation or even proctitis results from continued use.

Acidifying Salts

Ammonium chloride, ammonium nitrate and calcium chloride may produce diuresis by causing acidosis.[65] They are used at present only as a preliminary to the administration of mercurial diuretics. For according to Keith, Barrier and Whelan,[99] the acidifying salts, when so given, lead to a stronger diuretic action by the organic mercurials. The positive ion is metabolized while the excess chloride or nitrate ion is designed to carry sodium with it and consequently a proportionate amount of water. This mechanism is effective only the first day or two since there is a lag in the kidney's production of ammonia. Thereafter the ammonia combines with the chloride or other acidic ion and thus preserves sodium.

Two to 3 gm. (30 to 45 grains) of ammonium chloride three times daily are often administered orally for the two days preceding each injection of mercupurin. This is given in the form of compressed tablets of 0.4 gm. (6 grains) each (i.e., five to eight tablets three times daily) or of keratin coated capsules of 0.5 gm. (7½ grains) each (four to six tablets three times daily). In the intervals the ammonium chloride is discontinued to avoid nausea, vomiting or severe acidosis. The acidifying salts are contraindicated in patients with renal impairment. Prolonged use of ammonium chloride may cause a loss of intracellular as well as of extracellular fluid and the loss of potassium and phosphorus, i.e., dehydration as well as acidosis.

Xanthine Derivatives

The xanthine derivatives (purines) are now of limited use as diuretics because of the decisive superiority of the mercurial salts.[77] The xanthine derivatives may be worthy of trial when the mercurials are not tolerated. They possess the advantage that they may be taken orally. The exact mode of diuretic action of the xanthines is uncertain—increase in glomerular filtration, decrease in tubular reabsorption, increased blood flow and other mechanisms having been invoked.[13, 17] Following the intravenous administration of aminophylline to 45 patients with myocardial insufficiency Green and associates[80a] observed an average increase in cardiac output of 12 per cent with a range of plus 185 to minus 45 per cent. There was a more impressive increase in sodium and water excretion, especially the former. Renal clearance data indicated that the heightened excretion of sodium was due to a diminution in tubular reabsorption of this ion. Similarly Davis and Shock[35a] noted a variable increase in renal plasma flow and glomerular filtration rate with a more prominent and

sustained increase in sodium clearance. They therefore concluded that the latter was a result of a decreased tubular reabsorption of sodium.

The most effective diuretic of this group is theophylline (theocin), while theobromine, theobromine sodiosalicylate (diuretin) and caffeine have weaker actions.[117, 88] Theophylline ethylenediamine (aminophylline) in doses of 0.1 to 0.2 gm. three or four times daily, theocalcin (theobromine calcium salicylate) in doses of 1.0 gm. four times daily, thesodate (theobromine sodium acetate) in doses of 0.5 gm. four times daily and theophylline (theocin) 0.2 gm. four times daily, are among the commonly employed xanthine diuretics. Except in very occasional instances I have found no need for the xanthine diuretics when the mercurials can be used. However, the intravenous administration of aminophylline (0.25 gm. in 10 cc.) is very effective in controlling Cheyne-Stokes respiration associated with heart failure, and aminophylline suppositories containing 0.3 to 0.5 gm. of aminophylline, inserted before retiring, sometimes help to avoid paroxysms of nocturnal dyspnea.

Headache, nervousness, nausea and vomiting, abdominal cramps and diarrhea are common symptoms of sensitivity to the xanthine derivatives, especially if given in full therapeutic doses. Epilepsy is a contraindication to these drugs as they are said to irritate the cerebral cortex and precipitate convulsions in susceptible individuals. Sometimes the toxic symptoms of the purines can be prevented by combining each dose with ¼ to ¾ grain of phenobarbital. There is some evidence that the xanthine drugs may shorten the prothrombin time and increase the coagulability of the blood.[151]

Urea

When renal function is intact and other diuretics are no longer effective or cannot be given, urea is sometimes of distinct value as a diuretic. Satisfactory results have been reported by Crawford and McIntosh,[31] and by Miller and Feldman[130] who administered urea for long periods to the same patients. Important objections to this substance are the nauseating taste and the tendency to cause vomiting or extreme thirst. I have seen excellent clinical results.

Large doses of urea (45 to 90 gm. daily) must be given, usually in divided doses two to four times daily. Various efforts, not too successful, have been made to disguise its taste. It has been given in ice-cold water, in grape juice, in beer and in mixtures containing syrup of acacia. I have found urea to be taken best as an effervescent mixture made as follows.

℞		gm. or cc.
Urea	ʒ xvi	480.0
Saccharin	gr. xi	0.7
Potassium bicarbonate	ʒ xii	48.0
Citric acid	ʒ xiii ss	55.0
Tartaric acid	gr. xxx	2.0
Oil of peppermint	gtt. vi	0.4

M. Sig: One or two ounces dissolved in water three times daily. Drink slowly while effervescing.

Potassium Salts

Potassium salts have been used as diuretics, especially in combination with restriction of sodium chloride and fluids.[100] They are contraindicated in the presence of renal insufficiency. Potassium chloride is usually given in doses

of 2 to 4 gm. three times daily. To avoid gastric irritation it is usually given in enteric coated tablets. The cardiac toxicity of potassium salts is discussed on page 947.

OTHER DRUGS

Morphine. Next to digitalis and the mercurial diuretics, morphine is the most useful drug in the treatment of congestive heart failure. Its chief value and indication are in the management of the acute episodes associated with heart failure. Under such circumstances the therapeutic benefits of morphine are often brilliant and appear with striking speed. Morphine is administered for the relief of various forms of dyspnea, especially cardiac asthma and pulmonary edema, but also for severe dyspnea at rest and orthopnea associated with left-sided heart failure. Each dose of morphine should be individually ordered by the physician. Standing orders for repeated doses of opiates occasionally lead to serious overdosage or addiction. When dyspnea becomes persistent, the danger of morphine addiction must always be borne in mind; the drug must be either withheld or administered in small doses of 0.007 to 0.010 gm. (⅛ to ⅙ grain). Often these doses accomplish as much as can be expected from the use of morphine in cases of congestive heart failure. Even when care is exercised, morphine addiction is not rare because the unequalled, though temporary, relief obtained with this medicament leads to its continued usage.

The action of morphine, in so far as it relieves the symptoms of congestive heart failure, is not altogether certain. In the first place it depresses the respiratory center and interferes with the reflex which causes hyperventilation and dyspnea (see p. 108). At the same time it probably reduces the venous return to the heart, thereby diminishing the output of the right ventricle and consequently also the intense pulmonary congestion which is the basis of dyspnea. The diminution in ventilation reduces the work of the respiratory muscles, the oxygen consumption and therefore the work of the heart. The elimination of the patient's restlessness and anxiety is also an important effect of morphine, serving to improve the patient's comfort. On the unfavorable side is the antidiuretic effect of morphine in patients with heart failure,[55] but this is rarely of practical importance.

If the patient is suffering from moderate, continuous dyspnea at rest and orthopnea, he should be given 0.010 gm. (⅙ grain) of morphine or 5 minims of a 3 per cent aqueous solution hypodermically. This should be repeated morning and evening for a day or two until rest, digitalis and diuretics become effective. If the dyspnea is acute or severe, the dosage may have to be increased to 0.015 gm. (¼ grain) or 0.5 cc. (7½ minims) of the 3 per cent solution. If the patient is experiencing an attack of cardiac asthma or acute pulmonary edema, the dose should be between 0.015 and 0.020 gm. (¼ to ⅓ grain), depending on the severity of the attack. If immediate relief is urgent, the morphine should be given intramuscularly or 0.010 gm. (⅙ grain) should be injected intravenously, since the effect of morphine administered subcutaneously may not appear for one-half hour or more. If the patient had been suffering from recurrent attacks, small doses of morphine may be given prophylactically for a few days, usually before the patient retires in the evening. As a rule, 0.006 to 0.010 gm. (1/10 to ⅙ grain) of morphine hypodermically or 0.010 to 0.015 gm. (⅙ to ¼ grain) by mouth will suffice. But this is rarely necessary if digi-

talization, sodium restriction, mercurial diuretics and oxygen therapy are properly employed.

Codeine. Codeine sulfate in doses of 0.03 to 0.06 gm. (½ to 1 grain) hypodermically may occasionally be substituted satisfactorily for morphine in treating patients with chronic dyspnea. The chief value of this drug, however, is to control the cough due to pulmonary congestion and infection. The dose is 0.015 gm. (¼ grain) by mouth every three to four hours, but larger doses may be needed. Hycodan bitartrate in doses of 0.005 to 0.01 gm. ($\frac{1}{12}$ to ⅙ grain) is at least as effective in controlling cough and is less constipating than codeine. The medication should be given at night or repeated throughout the day if necessary.

Sedatives. Bromides in doses of 10 to 15 grains three times daily, chloral in doses of 5 to 15 grains, or combinations of the two in smaller dosage, or phenobarbital in doses of 0.015 to 0.03 gm. (¼ to ½ grain) three times daily are valuable as sedatives to allay restlessness and anxiety. Soporifics such as nembutal (1½ to 3 grains), seconal (1½ to 3 grains), ipral (2 to 4 grains) or veronal (5 to 10 grains) may be necessary to induce sleep. If insomnia is due to cough, codeine is necessary either in place of or in combination with soporifics.

Dicumarol. This drug has been administered in order to reduce the frequency of thromboembolic complications in heart failure and beneficial results have been reported.[182] (For method of administration see p. 882.)

Laxatives and Cathartics. When patients are ambulant, regular bowel action should be induced by habit formation with or without the aid of mineral oil. If this does not succeed or if patients are confined to bed, it is necessary to maintain regular bowel movements by mild cathartics or laxatives. Milk of magnesia (1 to 2 oz.), cascara sagrada (5 to 10 grains) or compound licorice powder (2 to 3 teaspoonfuls) is usually adequate. Magnesium sulfate (½ oz.), given every few days, has been found useful when patients are edematous, due theoretically to the loss of fluids associated with the catharsis. Cathartics acting on the colon should not be administered to patients receiving mercurial diuretics (see p. 196). Occasionally glycerin suppositories or small oil, saline or sodium bicarbonate enemas are useful, but they should be avoided if they weaken the patient unduly. An occasional colon irrigation when properly performed tires the patient less than an enema and relieves abdominal distention as well as constipation. Some patients undergo more physical and mental strain in trying to use the bedpan than when helped to the toilet or preferably to a commode at the side of the bed. For such patients the physician should employ his good judgment in determining whether the use of the bedpan is absolutely essential.

Brandy, sherry or nux vomica may be useful in treating patients who are depressed or suffer from weakness and anorexia. The alcoholic beverages may be especially helpful for elderly patients and those with coronary artery narrowing.

Hypertonic solutions of dextrose (50 cc. of 50 per cent, 125 cc. of 20 per cent or 250 cc. of 10 per cent solution) or of sucrose may be given intravenously in attacks of pulmonary edema and to promote diuresis. The carbohydrates have also been considered of therapeutic benefit because they improve the nutrition of the heart.

OXYGEN THERAPY

Oxygen, administered in high concentrations (40 to 50 per cent or higher), by means of special masks, tents or nasal catheter, may be of great symptomatic value in some cases of congestive heart failure. According to Barach and his associates,[4] who have been the most ardent advocates of this therapeutic measure, the depressed oxygen saturation of the arterial blood is restored to normal, dyspnea and cyanosis are relieved, the lactic acid content of the blood is diminished, diuresis effected and edema reduced. In my experience oxygen therapy is of limited value for the fundamental manifestations of congestive heart failure but may be of great benefit in treating associated symptoms or complications. It was shown above (p. 107) that the arterial blood of patients with congestive heart failure usually has a normal oxygen content so that further oxygen administration has no theoretical indication. Nevertheless many patients report subjective improvement with oxygen therapy. High concentrations of oxygen are indicated chiefly in the relatively small percentage of cases of congestive heart failure in which the oxygen content of the arterial blood is diminished. Usually, but not always, such cases are recognizable by the presence of cyanosis, but a therapeutic trial is desirable if there is any doubt. If oxygen must be administered continuously for many days, a tent is usually preferable to the mask since the administration of pure oxygen is irritating unless it is hydrated.

The cases of congestive heart failure in which oxygen therapy is indicated usually include the following:

(a) Congestive heart failure of rheumatic, arteriosclerotic, hypertensive or syphilitic etiology complicated by pulmonary lesions such as infarcts, pulmonary edema, lobar or bronchopneumonia.

(b) Congestive heart failure secondary to bronchopulmonary disease such as pulmonary emphysema, atelectasis or fibrosis or to kyphoscoliosis.

(c) Congestive heart failure associated with acute coronary thrombosis.

The administration of oxygen in the ordinary manner can hardly be expected to affect the arterial blood when it is normally saturated with oxygen. But the inhalation of oxygen or air under a positive pressure of 5 to 8 mm. Hg, as suggested by Barach and Martin,[4] may be beneficial even in such cases. For then the arterial oxygen content may be even greater than normal because the oxygen content of the plasma is increased, the oxygen combined with the hemoglobin being of course unchanged. Barach and Martin reported a clearing of pulmonary edema due to heart failure, presumably because the oxygen introduced offers an opposing pressure to the increased pulmonary capillary pressure. The oxygen causes a positive pressure within the chest which retards the entrance of blood into the right heart and therefore into the lungs.

PHLEBOTOMY (VENESECTION)

The removal of 350 to 1000 cc. of blood from the vein of a patient with congestive heart failure may rapidly and dramatically relieve dyspnea, orthopnea, cyanosis, systemic venous and hepatic engorgement. Phlebotomy is indicated chiefly when there is intense pulmonary engorgement (especially with pulmonary edema) due to left-sided heart failure. But it is also useful in cases of right-sided heart failure in which there is an extreme elevation of the venous

pressure and associated manifestations of systemic engorgement. Phlebotomy is often a life-saving measure when the patient suffers from acute pulmonary edema. Phlebotomy should also be performed when morphine and other therapeutic measures fail to control an attack or recurrent attacks of cardiac asthma.

In cases of right-sided heart failure with high venous pressure phlebotomy markedly reduces the pressure and often relieves symptoms, but the therapeutic results are rarely as striking as in cases of acute left-sided heart failure. When failure of the right side of the heart is secondary to pulmonary disease, phlebotomy is of dubious value. The symptomatic improvement after phlebotomy usually occurs with incredible speed, often when the needle is still in the vein.

The removal of less than 350 cc. of blood is rarely useful; larger amounts (up to 1000 cc.) should be withdrawn if no benefit is obtained, especially if the patient is a large person, has an increased blood volume, is hypertensive and if his blood has a satisfactory hemoglobin content. Phlebotomy is rarely justified if the patient is anemic. The phlebotomy should be performed by introducing a needle of large bore, such as is used for transfusions, connected with a 6 inch rubber tube by an adapter. A free flow should be obtained to avoid clotting. In an emergency the vein may have to be cut with a sterile scalpel.

Phlebotomy relieves the symptoms of congestive heart failure by reducing the circulating blood volume and consequently the venous return to the right side of the heart. This reduces the right ventricular output into the congested lung. The overloaded and failing left heart can then increase its cardiac output and relieve the pulmonary congestion.[94] In contrast to the emergency benefit of a needed phlebotomy is the subsequent regret at the loss of oxygen-carrying capacity of the blood. Therefore the indication for phlebotomy should be unequivocal. The cautious replacement of packed erythrocytes may have to be considered after the acute disturbance has been definitely controlled.

Tourniquets. Effects similar to phlebotomy may be obtained by the temporary application of tourniquets or blood pressure cuffs to all four extremities.[46] Dramatic improvement may follow this procedure in cases of paroxysmal dyspnea or pulmonary edema due to acute left ventricular failure.[107] This procedure should always be tried before a phlebotomy is performed.

MECHANICAL REMOVAL OF SEROUS EFFUSION AND EDEMA FLUID

Thoracentesis. It is often necessary to remove pleural effusions in cases of congestive heart failure. Thoracentesis is indicated when the effusion is large and is causing or contributing to dyspnea. It is sometimes difficult to ascertain the exact importance of a pleural effusion in the production of this symptom. When other therapeutic measures fail to relieve dyspnea, the removal of fluid from the chest is often indicated even when the size of the effusion does not appear to be very large. I use an airtight Potain set, by means of which the effusion is removed by suction into a bottle containing a partial vacuum. The patient lies on his side, with the side to be tapped uppermost. The needle is introduced posteriorly near the lower end of the effusion, the site of which has been localized by percussion or roentgen ray examination. Usually 500 to 1000 cc. but not more than 1500 cc. is removed. The procedure should be stopped if the patient becomes dyspneic, coughs or has pain in the shoulders.

Paracentesis. Only occasionally must ascitic fluid be removed in cases of congestive heart failure, and much more rarely since the use of the powerful

mercurial diuretics. Abdominal paracentesis is indicated when the peritoneal effusion is sufficient to cause symptoms such as dyspnea and distention despite all other medical therapy.

The patient, after voiding, sits up in bed with his feet hanging over the side of the bed onto a chair. The skin of the lower half of the abdomen is cleaned and the site of injection is sterilized and infiltrated with 2 per cent novocain. This site is in the linea alba midway between the umbilicus and symphysis pubis. Through the anesthetized area a 1 inch incision is made with a scalpel through the skin and fascia. A trocar and cannula are introduced by way of the incision through the fascia and into the abdominal cavity. The trocar is withdrawn and the ascitic fluid allowed to run out of the cannula and connecting tubes into large flasks. When the fluid stops draining, a sterile dressing and adhesive tape are placed over the incision and a broad, tight abdominal binder is applied.

Mechanical removal of subcutaneous edema is rarely necessary since mercurial diuretics have become available. If essential, the surgical insertion of Southey tubes or multiple incisions of the skin and subcutaneous tissue, usually of the legs, may effectively remove large quantities of fluid. Aseptic technic should be employed even though the danger of infection is less than in cases of nephrotic edema. The prophylactic administration of penicillin is justifiable. Massive edema of the scrotum should be treated by elevation with a Bellevue bridge and if necessary by multiple incisions.

TOTAL THYROIDECTOMY

Thyroidectomy was suggested as a means of treating congestive heart failure in the hope that by lowering the basal metabolism, i.e., the oxygen requirement and other needs of the tissues, the slow inadequate circulation would then be sufficient for the lesser demands made upon it. Furthermore the cardiac output and the work of the heart would be diminished. Subtotal thyroidectomy often gave brilliant results in cases associated with hyperthyroidism but was ineffective in other cases of congestive heart failure. Blumgart and his associates[14] suggested and performed total thyroidectomy for the treatment of congestive heart failure (and angina pectoris, for which see p. 398). The operation was restricted to those patients who were reasonably good surgical risks and suffered from intolerable congestive heart failure which had not responded to any or all of the measures discussed above. The results obtained have not been sufficiently striking to justify extensive use of the operation.[9, 14, 27, 26, 137] The procedure is becoming one of historical interest.

Thiouracil and Other Antithyroid Drugs. The same principle underlying total thyroidectomy for heart failure has suggested the use of antithyroid drugs to lower the metabolism and thus reduce the work of the heart. Sharpey-Schafer[157] reported prolongation of life by the use of 60 to 120 mg. daily of thiouracil in patients whose heart failure had not responded to the usual therapy. In seven to ten days there was a reduction in basal oxygen consumption, a fall in venous pressure, an augmentation of cardiac output and increased exercise tolerance. More recently Blumgart and associates[12a] employed radioactive iodine (I^{131}) in euthyroid patients with heart failure for the purpose of lowering their metabolism and the work imposed on the heart. The use of thiouracil and other drugs for heart failure is still experimental.

EMERGENCY TREATMENT OF ACUTE LEFT VENTRICULAR FAILURE (PULMONARY EDEMA)

An effort should be made to determine the underlying cause and precipitating factors as these may modify management. Thus if pulmonary edema is associated with acute coronary occlusion and shock, phlebotomy is rarely if ever part of the treatment. On the other hand, the indication for phlebotomy may be especially strong if the attack is precipitated by excessive intravenous infusions or transfusion. Rapid intravenous digitalization with ouabain may be the prime therapeutic agent if acute left ventricular failure results from the sudden onset of auricular fibrillation with a very rapid ventricular rate. When acute left ventricular failure is precipitated by some other paroxysmal tachycardia, the former may be most effectively controlled by checking the paroxysm with carotid sinus pressure, digitalization, quinidine or other agents as discussed in Chapter 12. In the presence of pneumonia or other serious infection prompt and adequate antibiotic therapy may be essential to the control of pulmonary edema.

In general, morphine is administered in doses of 10 to 20 mg. (1/6 to 1/3 grain) subcutaneously, intramuscularly, or occasionally intravenously, according to the urgency of the situation. Atropine may be combined in doses of 0.4 to 0.6 mg. (1/150 to 1/100 grain) if tachycardia is not a prominent feature. Coramine should be available if respiratory depression is excessive. The patient should be propped up high in bed or be permitted to sit with support while his feet hang down from the side of the bed. Oxygen therapy should be given promptly, preferably under slight positive pressure. Tourniquets should be applied serially to the four extremities with periods of release. If there is no contraindication, the patient should be rapidly digitalized, intravenously if the emergency demands it. If these measures are ineffective and there is evidence of an increased venous pressure and a high blood volume, a phlebotomy should be performed as discussed above. Other measures will be determined by the underlying disease and the precipitating factor. Prophylactic measures to prevent recurrence may include careful sodium restriction, the use of diuretics and the use of anticoagulants if the attack is precipitated by an embolism. (See also aminophylline, p. 482, and dextrose, p. 203.)

TREATMENT OF INTRACTABLE HEART FAILURE

Despite all the therapeutic measures detailed in this chapter, patients sometimes do not respond and the manifestations of heart failure persist or progress. In such cases it is important first of all to be certain that there is not some contributory or underlying condition which is remediable. In particular, in my experience, constrictive pericarditis and masked hyperthyroidism are overlooked and are responsible for persistent symptoms of heart failure. Not infrequently persistent heart failure is due to recurrent pulmonary emboli, and relief of the heart failure is obtained only after embolization is prevented by the use of anticoagulants or ligation of the veins in the lower extremities. Similarly a search should be made for anemia, avitaminosis, hypoproteinemia or infection, especially in the urinary or respiratory tract, and such abnormalities should be corrected if possible.

If no such underlying or contributory factor can be found or eliminated, a careful review should be made of the manner in which the various therapeutic

measures are being carried out. The limitation of the patient's activity or the completeness of his bed rest may be inadequate. Frequently the allowance of sodium intake is too generous or the patient is taking more sodium than has been permitted. The frequency of administration of mercurial diuretics may have to be increased, but this should be done with due regard for renal function and the electrolyte partition in the blood. Urea may be effective when the mercurials are not. The adequacy of digitalization should be reviewed. Only when all these measures are carried out may one presume that the disease process in the heart is too advanced to permit the relief of symptoms or improvement in circulatory function.

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10

ACUTE CIRCULATORY FAILURE: SHOCK, SYNCOPE AND SUDDEN DEATH

Acute and Chronic Circulatory Failure. Circulatory failure has been defined as the inability of the circulation to maintain an adequate minute volume blood flow to supply the needs of the tissues. In the preceding chapters I have discussed chronic circulatory failure (congestive heart failure) in which the deficiency in cardiac output is gradual in development and moderate in degree. Compensation is effected at first by cardiac enlargement and later by an increase in circulating blood volume. Many of the manifestations of chronic circulatory (congestive heart) failure are due to the inability of the heart to handle this compensatory increase in circulating blood volume.

This chapter is concerned with the more acute forms of circulatory failure in which the deficiency in cardiac output occurs so rapidly and is of such intense degree that it is impossible to restore a relatively normal output by the above compensations. Instead compensatory mechanisms are brought into play which redistribute the available low output in such a manner as to maintain an almost normal blood flow to vital organs at the expense of less important visceral and peripheral tissues. In large measure the different clinical pictures associated with acute and chronic circulatory failure are due to the differences in compensatory processes as well as to differences in the severity and speed of development of an inadequate cardiac output.

Shock, syncope and sudden death are forms of acute circulatory failure which differ in speed of onset of the circulatory failure, and in severity and reversibility. Sudden death occurs when the fall in cardiac output is so rapid and severe that vital medullary centers receive insufficient blood for survival. Syncope denotes a very acute circulatory failure in which the available compensatory mechanisms cannot maintain an adequate blood flow to the brain, but as a rule the cerebral ischemia is transient and reversible. In shock, the clinical picture develops rapidly but not as suddenly as in syncope. Several hours usually elapse before the dynamic processes responsible for shock evolve the distinctive clinical phenomena. Syncope and sudden death may also occur independently of acute circulatory failure.

Shock, syncope and sudden death are closely related in that one may merge into the other. Transient attacks of syncope may be followed by one which is fatal. Shock may occur with or without syncope.

SHOCK

Definition of Shock

The term *shock* was originally applied to a clinical syndrome, is still recognized and diagnosed on the basis of clinical phenomena and should be defined in terms of these phenomena. *Shock is a form of acute circulatory failure characterized by the rapid development of mental torpor and physical weakness, coldness of the extremities, cold moist skin, rapid and weak pulse and a fall in arterial blood pressure.*

Shock is said to be *reversible* in the early stages when circulatory function may be restored by appropriate therapy. Later there develops a stage of *irreversible shock* which progresses to fatal insufficiency despite all therapeutic measures.

Shock is sometimes used synonymously with peripheral circulatory insufficiency. However the clinical syndrome and physiological disturbances characterized as shock may be of cardiac or peripheral origin. Furthermore, since the circulation is an integral unit, it is misleading to refer to a generalized circulatory insufficiency as peripheral.

Classification of Shock

Shock may be classified according to physiologic disturbances which result in a diminished volume flow of blood (cardiac output). These include: (1) acute disturbances in (a) cardiac filling or (b) cardiac emptying which thereby sharply reduce the cardiac output; or (2) acute diminution in venous return due to a loss of blood, plasma or intravascular water, or to a pooling of blood in the small blood vessels.

Shock is also classified according to the causative clinical conditions, such as hemorrhagic shock, traumatic shock, burn shock, etc. These are incorporated in the following combined physiologic and clinical classification.

Acute Circulatory Failure

- A. Shock
- B. Syncope (p. 225).
- C. Sudden death (p. 228).

Shock

I. Acute Deficiency in Venous Return

- A. Deficient blood volume due to loss of blood or plasma.
  1. Hemorrhagic
  2. Traumatic
  3. Surgical or postoperative
  4. Burn shock
- B. Deficient blood volume due to dehydration.
  1. Vomiting and diarrhea (acute intestinal obstruction; cholera; acute diarrheas of infancy)
  2. Diabetic acidosis
  3. Addison's disease
  4. Heat exhaustion and syncope
- C. Pooling of blood in small vessels.
  (neurogenic?, vasogenic?, toxic?, reflex?, infectious?)
  1. Abdominal and testicular trauma
  2. Perforation of a hollow viscus

3. Spinal anesthesia
4. Acute pancreatic necrosis?
5. Acute diffuse peritonitis?
6. Acute febrile infections?
7. Toxic forms of shock?

II. Acute Deficiency in Cardiac Filling
   A. Mechanical hindrance.
      1. Sudden hemopericardium
      2. Acute pericardial effusions
   B. Severe tachycardias with abbreviated diastole.

III. Acute Deficiency in Cardiac Emptying
   A. Myocardial injury.
      1. Acute myocardial infarction
      2. Rupture of valve cusp, chorda, papillary muscle or of septum
      3. Diphtheritic or rheumatic myocarditis (?)
   B. Mechanical hindrance.
      1. Massive pulmonary embolism
      2. Ball-valve thrombus or tumor of left atrium
      3. Extreme mitral stenosis

Pathologic Physiology

Fundamental Mechanism. Despite the variety of clinical conditions and physiologic disturbances which may lead to shock, there is a fundamental mechanism common to all, which determines the clinical picture. This common denominator is a rapid and severe *reduction in cardiac output with consequent tissue anoxia.*

Shock is a dynamic process and its physiologic abnormalities may be considered in three stages: (1) initial disturbances, (2) compensatory mechanisms, (3) stage of irreversible shock.

1. *Initial Disturbances.* Like chronic circulatory failure, acute circulatory failure begins with an inability of the heart to maintain an adequate output of blood.[83, 32, 138] This may be caused by a reduction in blood volume and consequent diminution in venous return to the heart or it may be due to some cardiac or extracardiac disease which prevents the heart from filling or emptying properly.

The low cardiac output may be denoted clinically by the mental and physical weakness, low metabolism and occasional subnormal temperature. The weakness of the pulse and a low pulse pressure may be evidence of an extremely small stroke output. The tachycardia, usually present, is a well known cardiac compensation for a diminished stroke volume. Actual measurements have disclosed early and sharp reduction of cardiac output in experimental shock.[83, 129] By means of intracardiac catheterization and the use of the Fick principle Cournand and his associates[32] determined the cardiac output in clinical cases of shock due to skeletal trauma, hemorrhage or burns. Regardless of the type of injury they found the essential circulatory abnormality in these cases of shock to be a reduction in the cardiac output, averaging about 35 per cent.

2. *Compensatory Mechanisms.* The sudden and severe fall in cardiac output is a threat to all tissues, but especially to the brain, which is most sensitive to anoxia, and to the heart, which is also vital for survival. It is essential that

the reduced volume flow available be redistributed in favor of the brain and heart and at the expense of the peripheral tissues and splanchnic viscera. Furthermore an adequate blood pressure must be maintained in order to perfuse these vital organs. Both objectives can be and are accomplished by widespread vasoconstriction. Because of the relatively poor vasomotor innervation of the cerebral and coronary arteries, their blood flow is relatively little affected by the generalized vasoconstrictor mechanism. On the other hand vasoconstriction in the skin and splanchnic vessels so increases the peripheral resistance that blood pressure is maintained at much higher levels than would otherwise be possible with the diminished cardiac output.

In contrast with chronic circulatory failure (congestive heart failure) vasoconstriction and redistribution of blood flow is the major compensation for shock; a compensatory increase in blood volume is attempted but is of negligible significance. In chronic circulatory failure, there is adequate time to increase the blood volume sufficiently to restore a relatively normal output in the early stages; vasoconstriction also occurs but is of negligible importance.

The occurrence of widespread vasoconstriction and redistribution of blood has been demonstrated by many clinical and experimental observations.[12, 158, 15]

Perhaps the most striking evidence of intense vasoconstriction is found in the skin, which is extremely cold and moist, especially in the distal parts of the circulation such as the extremities and tips of the nose. Baldes and associates[11] found that when shock was induced in dogs by intestinal manipulation, there was as much as 75 per cent reduction in blood flow through the femoral artery even though the blood pressure was maintained at normal levels. Similar evidence of disproportionate vasoconstriction may be found in the experiments of Erlanger, Gesell and Gasser[48] who observed a 60 per cent reduction in the blood flow through the salivary gland, following only a 10 per cent reduction in circulating blood volume without change in arterial pressure. In clinical cases of surgical shock Freeman, Shaw and Snyder,[60] with the aid of the venous occlusion plethysmograph, observed a striking diminution in blood flow through the hand and a loss of the normal ability to increase this flow by warming or by applying and releasing a tourniquet. The fact that the blood flow (cardiac output) in experimental and clinical shock generally declines before the blood pressure falls, also indicates the early development of vasoconstriction.[83, 74, 127]

Of special interest are the findings that in the early phase of shock there is a decline in renal blood flow which is even greater than the decline in cardiac output.[94, 127, 157] Thus while the total blood flow decreases to about half of normal, the renal blood flow, which is normally 20 to 25 per cent of the total, is reduced to one tenth or less of its usual amount.[94]

The existence and significance of renal shunts[155] through the renal medulla in cases of shock is undetermined. Apparently, in acute as in chronic circulatory failure, the kidneys play an important role in the defense of the organism,[72] either in restoration of cardiac output by increasing the blood volume and venous return, or by a vasoconstrictive redistribution of an inadequate blood flow and maintenance of blood pressure.

The mechanisms by which vasoconstriction, redistribution of blood and maintenance of blood pressure are effected are probably multiple. The role of the adrenal medulla and sympathetic nervous system is best known. That sympathetic vasoconstriction is important in producing the shock syndrome is

denoted by the cold sweat in human cases, and by the difficulty in producing experimental shock after bilateral sympathectomy.[59] There is also evidence that reflexes by way of the carotid sinus and vasomotor center, adrenal cortical hormones, and renin-like or other pressor substances released from the kidney in response to ischemia[142, 37, 145] participate in the compensations for acute circulatory failure.

At the same time that these vasoconstrictive phenomena are occurring in various organs and tissues during the compensatory stage of shock the blood pressure may decline but is still adequate for cerebral and coronary blood flow. There may be mental apathy but consciousness and coherence are usual. There is no clinical or electrocardiographic evidence of significant cardiac damage or of an inability of the heart to handle the venous return.[166]

3. *Stage of Irreversible Shock.* Prolonged, severe shock eventually leads to failure of these compensatory mechanisms, with consequent progressive decline in cardiac output and blood pressure, profound tissue anoxia involving also the heart and brain, and death. During the uncompensated or irreversible stage of shock, restoration of blood volume and other therapeutic measures, which are usually effective in the early stages, are incapable of altering this baneful series of events.

During the stage of irreversible shock, the continued fall in cardiac output and in blood pressure occurs even when there is no significant further reduction in blood volume. The circulation time becomes greatly prolonged. These findings suggest that the decline in cardiac output in this stage is due to peripheral stasis, and the inability to build an adequate blood pressure is due both to the falling output and the failure to maintain compensatory vasoconstriction. In other words irreversible shock is associated with a reduction in peripheral resistance and a pooling of blood in small vessels.

These concepts are supported by direct observations of capillaries in various animals with induced shock. In the compensated stage there is accentuated vasoconstrictor activity of metarterioles and precapillary sphincters, and hyperreactivity to small doses of epinephrine. In the irreversible stage there is a diminution in vasomotor activity with dilatation of arterioles and venules, diminution or absence of response to epinephrine, capillary stagnation and eventual cessation of blood flow.[172, 26, 91] Postmortem observations have disclosed generalized capillary dilatation and stasis and packing with erythrocytes. Studies of blood volume in experimental shock with radioactive isotopes disclosed evidence of widespread "trapping" of red cells within the minute vessels of all the organs of the body.[66] Thus in the irreversible stage of shock, pooling of blood in atonic small vessels intensifies the previous deficiency in venous return and cardiac output and nullifies the compensatory mechanisms which maintained a sufficient blood pressure and blood flow to vital organs. However, these secondary and terminal occurrences should not be confused with the initiating causes of shock.

The actual cause of irreversibility of shock is uncertain. Metabolic or toxic changes, induced in the organs which suffered from prolonged and intense vasoconstrictive anoxia during the compensated period of shock, are the most probable factors inducing irreversible shock. The importance of compensatory vasoconstriction in causing irreversible shock is supported by the observation that the occurrence of irreversible hemorrhagic shock in experimental animals was delayed and its incidence diminished when dibenamine, a

sympatholytic drug, was administered twenty hours before the shock-producing venesection.[168] The vascular atony and capillary stasis and trapping of blood may be due to the direct or neurogenic effects of such factors.

Of the organs suffering from vasoconstriction, the *liver* is most sensitive to anoxia, perhaps because of the relatively low normal oxygen content in the portal vein, its chief source of supply. There is considerable evidence of hepatic dysfunction in shock as denoted by the rise in blood amino nitrogen[45, 140] and other chemical changes (p. 222). Further evidence of the role of liver damage in irreversible shock is seen in the observation that irreversibility of hemorrhagic shock in dogs can be prevented by viviperfusion of the liver (by way of the splenic vein) with normal donor's blood.[57] Similar arterial transfusion into the jugular vein of the shocked animals was ineffective. Shorr and his associates[145] reported the finding of a humoral substance ("vasodepressor material"—VDM*), elaborated essentially by skeletal muscles and liver after prolonged shock and responsible for the atony and stasis found in small blood vessels in the irreversible stage. When blood removed from animals early in shock was injected into normal animals, it induced augmentation of amplitude and rate of vasomotion of metarterioles and heightened sensitivity to epinephrine as described above.[25] Similarly injection of blood from animals late in shock caused a fall in blood pressure and diminished response to epinephrine as described for the originally shocked animals. These observations indicated that the vasotropic substances in experimental shock were bloodborne.

The *kidney* has been mentioned as suffering from intense vasoconstriction and reduction in blood flow during the compensated stage of shock. This may lead to organic renal changes, especially in the tubules, if shock is severe and prolonged (lower nephron nephrosis[102]). Oliguria or anuria, urine of low specific gravity, low urea clearance and uremia may result. Such renal failure may develop as a result of prolonged anoxemia and organic changes, even after normal circulatory function has been reestablished, as in the so-called crush syndrome.[21] Renal failure may contribute to the acidosis of shock and may itself be responsible for death. But it is unlikely that renal anoxia is responsible for the irreversible stage of shock.

Anoxia of the *skeletal muscles* during prolonged shock gives rise to metabolic disturbances which contribute to the alterations in blood chemical findings (p. 222).[44] But the possible role of these disturbances in irreversible shock is uncertain.

The *heart* itself, which is fairly well supplied with blood during the compensated stage, may suffer if shock is severe and prolonged.[166] Depression in myocardial function may thereby contribute to the circulatory debacle that occurs during irreversible shock. Wiggers and Werle[167] showed that the capacity of the ventricles to respond to a given venous pressure was reduced in animals with hemorrhagic shock. Kohlstaedt and Page[92] observed a stage of cardiac constriction followed by one of cardiac dilatation corresponding to similar peripheral vascular changes in progressive shock. Prinzmetal and Bergman[130] observed a maximal increase in the number of open capillaries in the hearts of rats with burn shock and concluded that the heart in shock suffers from decreased coronary flow, capillary atony with retention of metabolites and myocardial dehydration. In cases of clinical shock, e. g. after acute hemorrhage or

* Identified as ferritin.

massive pulmonary embolism, we have observed myocardial necrosis or infarction without coronary occlusion, due undoubtedly to functional coronary insufficiency.[62] Despite these evidences of late myocardial damage in severe shock, it is probable that they are the consequences and not the cause of irreversible shock.

Etiology and Pathogenesis

Acute Deficiency in Venous Return Caused by Loss of Blood or Plasma Volume. Under this heading are included cases of shock due to hemorrhage, trauma, burns, surgery, etc., in which the initiating cause is a reduction in circulating blood volume. Harrison[77] refers to this group as hematogenic shock and Fishberg[55] terms it oligemic shock. The reduction in circulating blood volume results in a diminution in the venous return and consequently in a decline in cardiac output. Diminished venous return is denoted in clinical shock by the collapsed superficial veins and by the finding of very low atrial pressures by cardiac catheterization.[32] A progressive increase in the circulation time[120, 159, 160] indicates that slowing of blood flow later accentuates the decline in venous return.

The classic studies of Robertson and Bock[134] and of Keith[87] during World War I disclosed striking reductions in circulating blood volume in cases of traumatic or wound shock, and a definite relationship between the reduction in blood volume and the severity of shock. Numerous other experimental and clinical studies have demonstrated the close causal relationship between reduction in blood volume and the development of hemorrhagic, traumatic and burn shock. Recent studies of traumatic shock in dogs revealed that the clinical picture of shock appeared when there was at least a 30 per cent reduction in blood volume, and in dogs that succumbed the reduction was 40 per cent or more.[71] In clinical studies of traumatic shock, similar pronounced declines in circulating blood volume (30 to 40 per cent below normal) were discovered with the aid of the blue dye T-1824.[32, 50, 22, 118] Practically, this denotes that clinical shock follows the rapid loss of about 1.5 to 2.0 liters of blood. Similar reductions in blood volume occur in burn shock.[156, 27, 86] The latter usually develops when more than 10 per cent of the cutaneous surface is involved.

Theories of Reduction in Blood Volume. *Local Fluid Loss.* The cause of the reduction in blood volume is usually clear when there is massive external bleeding. In surgical or postoperative shock,[81] the amount of blood loss during operation is much greater than was formerly recognized. Preoperative and postoperative vomiting or bleeding and loss of fluids from excessive perspiration are factors contributing to the reduction in blood volume.

In recent years it has become increasingly manifest that gross reductions in blood volume in cases of wound, skeletal and burn shock may be due entirely or almost entirely to the extravasation of blood or plasma out of the blood stream and into the injured area. When shock was induced in animals by trauma to a hind leg, comparative weights of the injured and normal legs disclosed that the loss of blood and plasma into the injured leg was sufficiently large to account for the reduction in blood volume and occurrence of shock.[14] Similarly, shock induced experimentally by intestinal manipulation or by burns could be explained by the local loss of fluid in the burned or damaged tissues.[14, 156, 74] These findings have been confirmed by Parsons and Phemister[121]

and others,[125] and more recently by Nickerson[116] and by Ashworth et al.,[4] who demonstrated quantitatively that the fluid loss was equal to the observed reduction in circulating blood volume. Of interest also in this connection are the observations of Duncan and Blalock[38] that shock does not develop if local fluid loss after trauma is prevented, e. g. by application of a cast.

Toxic Factors. The production of circulatory failure with a fall in blood pressure and reduction in blood volume following the injection of histamine[34] suggested that toxic substances liberated by injured tissues might be responsible for shock. Shock has been produced by a variety of extracts of normal and traumatized tissues but the results are not consistent and the type of shock induced differs in fundamental respects from traumatic shock.[14, 109, 106, 70, 89] Similarly cross circulation experiments in which the production of shock was attempted by transfusion of blood from shocked to normal dogs have usually been unsuccessful or insufficiently controlled.[14, 88, 69]

Several variants of the toxic theory of shock have been recently proposed. It has been shown that, at least in experimental traumatic shock, bacterial toxins may be important, especially the toxins of clostridia.[9, 131] The reported appearance of a vasodepressor material from shocked liver and skeletal muscle has been mentioned.[145] Profound metabolic changes with alteration of the chemical pattern of the blood have been reported,[44] but these are secondary factors which may enhance the progress of shock and lead to irreversibility, but do not initiate the disorder. Retention of potassium with hyperpotassemia may occasionally be a contributing factor in causing death,[170] but is not of primary importance in the etiology of shock.

Nervous factors have been invoked as the possible cause of shock, but the weight of evidence is strongly opposed to the concept that traumatic shock of the type under discussion is induced by nervous reflexes.[152, 126, 159] The occurrence of so-called primary or neurogenic shock is discussed below.

The theory of *generalized capillary permeability* with leakage of fluid from the circulation, as contrasted with local extravasation in the injured area, has been championed most vigorously by Moon.[109] This was based essentially on (1) pathologic findings in shock which represent terminal changes, (2) analogy with the findings in histamine shock which differs fundamentally from traumatic shock, and (3) an exaggerated emphasis upon hemoconcentration of blood, which has recently been shown to be absent except in shock due to burns or abdominal injuries with peritonitis.[32] On the other hand there is adequate evidence that the reduction in blood volume can be explained by local fluid loss[14, 125]; studies with radioactive sodium show a decrease in transcapillary exchange instead of the increase to be anticipated if capillary permeability were enhanced[65]; and a study of radioactive proteins in hemorrhagic and tourniquet shock[53] and of radioactive dyes in burn shock[31] discloses no evidence of generalized capillary leakage. The theory of generalized capillary leakage no longer appears tenable.

Acute Deficiency in Blood Volume and Venous Return Due to Dehydration. In this etiologic type of shock, a deficient venous return and cardiac output are likewise due to a reduction in circulating blood volume; the latter is caused, not by a loss of blood or plasma, but by an excessive loss of fluid and electrolytes by way of the kidney, gastrointestinal tract or skin. This type of shock is sometimes termed "medical shock."[7] Because the loss of blood volume is due to or concomitant with a loss of sodium, the clinical picture of shock is complicated

or overshadowed by the effects of loss of base (acidosis) and tissue dehydration.

In the intense *gastroenteritis* of infancy, in *cholera* and in *high intestinal obstruction* with vomiting, the excessive loss of fluid is obvious, while oral replacement is either impossible or grossly inadequate. With vomiting there is chiefly loss of chlorides with some sodium, and with diarrhea chiefly a loss of sodium. Since the extracellular water content is essentially a function of dissolved electrolytes,[63] such loss of ions is associated with a reduction in circulating blood volume. Actual diminution of blood volume due to diarrheas of infancy has been noted.[35, 107]

In *diabetic acidosis,* there is an excessive loss of sodium through the kidneys, both as sodium chloride and in combination with ketone radicles.[8] This results in an excessive loss of fluids which are not replaced because of nausea or vomiting, and consequently in a reduction of blood volume and shock.[124]

In *Addison's disease,* deficiency of the sodium regulating factor of the adrenal cortex leads to excessive renal excretion of sodium, a corresponding loss of fluid and a reduction in circulating blood volume.[101] The fluid loss is often intensified by diarrhea and vomiting, which occur during crises. The clinical picture of shock in Addison's disease is complicated not only by dehydration but by disturbance in carbohydrate metabolism, by retention of potassium, and by fever and sensitivity to mild infections.

Acute Deficiency in Venous Return Due to Pooling of Blood in Small Vessels. A deficiency in venous return and in cardiac output with a consequent clinical picture of shock can result from pooling or stagnation of blood in small vessels and without any external loss of blood or plasma. Such pooling may result from direct impairment of vascular tone with consequent vasodilatation (vasogenic shock of Harrison[77]) or from reflex or neurogenic vasodilatation (neurogenic shock).

The former is represented by *histamine shock* and perhaps various types of chemical, toxic or anaphylactic shock. The neurogenic type of shock is represented by the almost immediate collapse which follows a bullet wound, abdominal blow ("solax plexus" punch), testicular injury or perforation of a hollow viscus. This type of shock is also classified as "primary" shock because of its early onset after trauma as compared with the "secondary" shock or wound shock which we have been discussing and which usually develops after several hours. Syncope (p. 225) is common in this neurogenic type of shock.

This form of shock differs from the previous groups also in that a fall in arterial blood pressure (due to vasodilatation) precedes the decline in cardiac output. This was observed particularly in the shock following experimental spinal anesthesia.[20] According to the observations of Smith and collaborators[146] the relaxation involves the postarteriolar vessels, i. e. the capillaries and small venules.

There is uncertainty as to the mechanism of shock in such conditions as acute pancreatic necrosis, large peripheral embolism, acute diffuse peritonitis and acute infections.[40, 161, 58] Direct or reflex vasodilatation due to toxic substances, reflex vasodilatation due to neurogenic impulses and in some cases also local extravasation of fluid and dehydration may be concerned.

Acute Deficiency in Cardiac Filling. This group comprises cases of shock due to the sudden development of inflammatory pericardial effusion or hemopericardium which compresses the heart and prevents its filling (cardiac tamponade). Occasionally the sudden development of an extreme tachycardia

likewise prevents cardiac filling by abbreviating diastole. In this group there is often a simultaneous, initial pooling of blood proximal (upstream) to the right chambers of the heart, i. e. in the systemic circulation. Incomplete filling causes a sharp drop in cardiac output and shock or syncope.[12]

A more detailed discussion of acute cardiac tamponade can be found on p. 507 and of tachycardias on p. 263.

Acute Deficiency in Cardiac Emptying. There is a primary reduction in cardiac output in these cases either because of some mechanical obstruction (ball-valve thrombus, massive pulmonary embolism) or because of sudden impairment of cardiac function (acute myocardial infarction). This type of acute circulatory failure is sometimes termed cardiac shock. The clinical picture is essentially identical with that of shock due to an acute reduction in venous return. The circulation time is usually prolonged but there are scanty data as to the blood volume.

In cases of shock due to acute myocardial infarction there is a tendency to pooling of blood proximal (upstream) to the left cardiac chambers. This often results in acute pulmonary congestion (left ventricular failure) in association with shock. When acute myocardial infarction occurs in a previously insufficient heart, there may be a combined picture of congestive heart failure and shock.

The individual conditions responsible for this etiologic type of shock are discussed elsewhere under their respective headings.

Pathology of Shock

Since shock represents a dynamic progression of physiologic abnormalities, the reported pathologic findings in experimental and clinical shock must be viewed as terminal changes in fatal cases.

During abdominal operations on patients in shock the viscera and peritoneum are often found to be remarkably pale.[23] On the other hand, Gasser, Erlanger and Meek[64] observed great dilatation of capillaries and venules, packed with red blood cells, in various types of experimental shock. More recently Moon and Kennedy[110] and Moon[109] have repeatedly emphasized the occurrence of diffuse capillary congestion, edema, effusions and petechial hemorrhages in the viscera, following experimental and clinical shock.

Gastric and intestinal ulcers have been repeatedly observed in cases of shock due to histamine, following adrenalectomy, due to burns,[74] and in patients who succumbed after major operative procedures or diseases associated with shock.[122] The pathologic findings in the latter group were interpreted as the result of intense vasoconstriction.[90]

Clinical Features of Shock

General Appearance and Behavior. The patient may be restless or he may lie quietly, apathetic and oblivious of his surroundings. Restlessness is common in the early stages of acute hemorrhage. Occasionally the patient in shock is able to drive himself home or to a physician's office or he walks into a hospital emergency room. Occasionally he is found wandering aimlessly about the scene of his injury.

More often the patient is extremely weak and incapable of any but the mildest physical exertion. Mental torpor corresponds with his physical lethargy. His responses are feeble and hesitant but usually coherent. Advancing shock is char-

acterized by progressive physical and mental exhaustion bordering on coma. Sensation is dulled and responses become incoherent or absent.

The Skin. The skin is *pale and cold*. In very severe shock the pale skin is mottled bluish-red (cutis marmorata) due to irregular congestion and constriction of superficial blood vessels. The coldness and pallor of the skin are most pronounced in the hands, feet and tip of the nose. Occasionally, as in shock due to a ball-valve thrombus or extreme mitral stenosis, I have seen intense cyanosis with foci of necrosis in these peripheral regions. The skin temperature may be low even when the patient is febrile.

A *grayish cyanosis* is frequent. *Excessive perspiration* renders the skin clammy as well as cold.

The *rectal temperature* may be subnormal due to a low rate of metabolism and loss of heat through perspiration.

The Pulse. A *rapid, weak pulse* is characteristic. Terminally there may be a bradycardia. A rapid pulse usually appears before the decline in blood pressure and may be of diagnostic value.

The Respiration. This is variable according to the etiologic factor. Often it is deep and rapid due to increasing acidosis.

The Blood Pressure. *Hypotension* is characteristic of shock but the blood pressure may remain normal at the onset of shock when a significant decline in cardiac output has already occurred.[11] The compensatory vasoconstriction occasionally is so intense that the blood pressure is temporarily above normal.[33, 169] However, a progressive decline in blood pressure is the rule. Usually the blood pressure is below 90 mm. Hg and in very severe and in irreversible shock below 70. The *pulse pressure* is reduced.

The Heart. In the cases of shock due to a deficient venous return there is no evidence of cardiac impairment. Evidence of myocardial depression in advanced experimental shock has been discussed.

The Veins. The superficial veins are collapsed. The difficulty of inserting a needle is well known. The venous pressure is low, 1 to 2 cm., and cardiac catheterization has disclosed that the right atrial pressure is likewise low.[32] Occasionally the cervical veins are prominent when the antecubitals are collapsed, presumably due to peripheral vasoconstriction, with redistribution of blood in favor of the head.[54]

The Urine. The urinary output is diminished and in severe shock there may be complete anuria (p. 217). Renal clearance studies show a depression of renal blood flow and of glomerular filtration. Despite a low urinary output, the specific gravity may be low.

The Blood. A *leukocytosis* is common, especially in hemorrhagic shock, but leukopenia may be present in severe shock.[23]

Hemoconcentration is usual in shock due to burns, to dehydration and in some cases of abdominal injuries. *Hemodilution* is observed in shock due to hemorrhage, skeletal trauma and crushing wounds.[32]

Hyperglycemia occurs early and is believed to result from a compensatory secretion of epinephrine.

Acidosis[23] is usual in well-developed shock. It is due to an accumulation of lactic, phosphoric and pyruvic acids in the blood. Lactic and pyruvic acids increase because of excessive production in the skeletal muscles and because of impairment of liver function.[45, 3] The increase in phosphates is due chiefly to impaired renal excretion. The accumulation of fixed acids releases bicar-

bonate which is eliminated as carbon dioxide through the respiratory tract. A diminution in alkaline reserve, denoted by a low carbon dioxide combining power, results from loss of sodium excreted in combination with the fixed acids. The pH of the blood may be significantly diminished but is usually relatively normal.

Urea and nonprotein nitrogen are elevated because of increased catabolism and deficient renal excretion.[153, 28]

An *elevation of alpha amino nitrogen* results from increased catabolism and impaired deamination by the liver.[140, 80]

The *arterial oxygen* is usually normal until preterminally. The *venous oxygen content* falls progressively.[10, 129] The *arteriovenous oxygen difference* is increased. This is indicative of a prolonged circulation time which compensates for the low cardiac output by permitting a more complete oxygen extraction by the tissues.

Potassium may be increased because of increased protein catabolism, impaired renal excretion or adrenal cortical deficiency.[143]

Treatment of Shock

Prophylaxis. Many types of shock are easily preventable. In *surgical procedures* preoperative correction of dehydration and anemia, omission of drastic purgation, restoration of glycogen reserves in the liver, elimination of excessive sweating, careful hemostasis and minimal handling of tissues during the operation, expert administration of anesthesia and avoidance of long operations will minimize the incidence of postoperative shock. Traumatic shock may be avoided by prompt control of bleeding with the aid of pressure, ligature, (or tourniquet, if necessary,) and especially by rapid transportation to a hospital where more definitive measures can be carried out. Protection from cold and pain and the rapid splinting of injured parts are also valuable prophylactic measures.

Early Treatment. Successful treatment of shock must begin early, before the irreversible stage is reached. This means early diagnosis. The probability of shock should be gauged from the severity of trauma, the extent of a burn, outward evidences of bleeding, the nature of an operation or of other circumstances associated with the causative condition; if these circumstances suggest that shock is probable, treatment should be instituted before there are frank clinical evidences of shock.

Treatment. The *causative condition* should be corrected. This may mean the ligation of bleeding vessels, setting of fractures, closure of a perforated viscus, drainage of a pericardial effusion, removal of an atrial tumor, administration of adrenal cortical extract and sodium in Addison's disease, or of insulin in diabetic acidosis.

Transfusion of whole blood is the mainstay of treatment in shock due to hemorrhage or trauma.[150, 147] It has also been recommended in the treatment of burns.[49, 1] Blood should be given early and in adequate amounts. The latter can be gauged by observation of the clinical response and determinations of the blood count, hematocrit and blood volume. In the presence of shock, recovery usually requires at least 1000 to 1500 cc. of blood. Arterial (radial or aortic) transfusion has been recommended in very severe cases of shock.[92, 85] Care should be taken to avoid the precipitation of pulmonary edema by too rapid or excessive transfusions (or infusions of plasma or saline), especially

in elderly individuals and in those with known cardiac disease. In cases of shock with extreme oliguria or anuria the parenteral administration of fluids must be given with particular caution because of the hazard of congestive heart failure. Proper cross-matching of blood with respect to type and Rh factor is essential.

Plasma and other blood substitutes including the newer preparations of gelatin are relatively much less satisfactory in traumatic or surgical shock. Plasma is indicated in the early stages of burn shock, in which there is relatively little loss of erythrocytes and the hematocrit is elevated.[43, 13, 98] As a rough guide, 75 cc. of plasma is given in the first twenty-four hours for each per cent of body surface burned and somewhat less on the second day. Thereafter the amount is gauged by the clinical condition of the patient, and by determinations of blood counts, hematocrit, specific gravity and chemical examinations of the blood.[74, 30, 75] Fluid and electrolytes are given parenterally or orally to supplement the plasma. Good results have been reported in the treatment of burn shock with very large amounts of sodium lactate.[139, 56]

Dextran, which is a polydispersoid glycose polymer with a molecular weight conforming to that of albumin (about 100,000),[154a] has recently been recommended and fairly widely used in Sweden as a plasma substitute for the prevention and treatment of surgical and other forms of shock. Dextran is not pyrogenic, antigenic or toxic and most of it is removed slowly from the blood stream in four to seven days.[19a] Unlike most of the other plasma substitutes, dextran is normally metabolized. In cases of shock it is said to produce a prompt and lasting increase in blood pressure. It has been administered intravenously as a 6 per cent dextran solution in 0.9 per cent sodium chloride.

Crystalloid solutions, especially an isotonic (0.85 per cent) solution of sodium chloride or other sodium-containing solutions, are given intravenously or subcutaneously until blood and plasma are obtained, to supplement plasma in burn shock, and in the treatment of shock due to dehydration. Potassium salts may be necessary in the dehydration diarrhea of infants.[68]

Alkalis, in the form of a 5 per cent solution of sodium bicarbonate or a 1/6 molar lactate solution, may be given to correct the acidosis associated with shock. About 60 cc. of the 1/6 molar lactate per kg. body weight increases the CO_2 combining power of the blood 25 to 35 volumes per 100 cc.

Oxygen is of doubtful value in most cases of shock since the arterial oxygen is normal. It is useful in cases with pulmonary injuries or complications and in cases of burns with exposure to noxious fumes.

Warmth. Conservation of body heat with the aid of moderate coverings is desirable, but the application of external heat may be detrimental.[16, 38]

Morphine may be indicated for the relief of pain and thus indirectly to treat shock. It is rarely necessary and should be given cautiously after shock is developed.

Lowering of the head (Trendelenburg position) is useful in some types of shock.

Vasoconstrictor drugs are not indicated except in cases of neurogenic shock in which pooling of blood results from peripheral vasodilatation. Paredrine (10 to 20 mg. intramuscularly or 5 to 10 mg. intravenously) and neo-synephrine (5 mg. subcutaneously) are useful in the shock which may follow spinal anesthesia.

Digitalis is not indicated for the treatment of shock.

Adrenal cortical hormone has been reported to be useful in the prevention of experimental shock and the treatment of clinical shock.[123, 144, 117] Its value, other than in cases of shock due to adrenal cortical insufficiency, is unproven.

SYNCOPE

Syncope is characterized by a sudden and usually unexpected loss of consciousness and of locomotion. If the subject is upright he falls. Fainting, swooning and neurocirculatory failure are used synonymously with syncope. Certain instances of primary or neurogenic shock are associated with syncope.

Syncope is usually a form of hyperacute circulatory failure due to extreme ischemia or anoxia of the brain. It may also be caused by severe traumatic, metabolic or psychologic disturbances. As a rule syncope results from an extreme fall in blood pressure or pronounced slowing or standstill of the heart. The erect position, extreme exertion and environmental heat are usually predisposing or precipitating factors.

1. Vasodepressor Syncope. (a) *Psychic or Neurogenic Fainting.* This is the simple faint of psychic or reflex (neurogenic) origin, the so-called vasovagal syncope.[99] Fright, pain or other powerful emotions, the sight of blood, operations, etc., the experience of physiologic tests or instrumentation are among the causes of this type of fainting. Syncope in these cases is the result of a sharp decline in blood pressure, possibly mediated by way of the carotid sinus. It always occurs when the patient is in the erect position. There are premonitory symptoms such as weakness, nausea, sweating, pallor. Slowing of the pulse and heart block may develop but these are not responsible for the syncope.

This type of vasodepressor syncope is observed in the acute circulatory collapse which sometimes follows moderate venesections (300 to 900 cc. blood), e. g. occasionally in healthy blood donors.[128, 162] The cardiac output may be only slightly diminished or unchanged since reflex peripheral vasodilatation results in an increased speed of circulation whereby a relatively normal venous return is maintained. Syncope is due to an extreme fall in blood pressure associated with a corresponding diminution in peripheral resistance. This is to be contrasted with the sharp fall in cardiac output and the clinical picture of shock which follows the loss of larger amounts of blood (1500 to 2000 cc. or more).[19]

Under the heading vasodepressor syncope are also included cases of primary shock (p. 220), fainting with onset of acute infections, with strenuous exercise, during pregnancy, and after vasodilating drugs such as nitrites and nitroglycerin.

(b) *Carotid Sinus Syndrome.* Infrequently, spontaneous attacks of unconsciousness result from hypersensitivity of the carotid sinus.[164, 52] These attacks can be reproduced by pressure over the carotid sinus. In normal persons such pressure causes only a slight reduction in pulse rate (less than 6 beats per minute) and only a slight reduction in blood pressure (less than 10 mm. Hg). The carotid sinus tends to become sensitive in individuals past middle age, and especially in those with hypertension or arteriosclerosis. In subjects with a hypersensitive carotid sinus the slightest pressure, such as that due to the passage of a razor over the neck, bending or turning of the head in certain positions, a high or tight collar, may induce dizziness or syncope. Similar attacks rarely result from the pressure of an enlarged cervical gland or tumor.[108] Tests of carotid sinus sensitivity should be performed with caution.[105, 5]

Carotid sinus hypersensitivity may result predominantly in (a) vasodepression with a sharp fall in blood pressure, (b) cardiac slowing, cardiac standstill or heart block with or without ventricular standstill or (c) reflex cerebral ischemia with convulsions and focal neurologic signs. Each reaction type may cause syncope. The last or cerebral type of carotid sinus syncope is unaccompanied by changes in pulse or blood pressure and is associated with slow waves in the electroencephalogram.

Rarely a lesion on an afferent vagal arc induces syncope by a vagovagal reflex by way of the carotid sinus. In the case reported by Weiss and Ferris[165] a patient with an esophageal traction diverticulum experienced attacks of fainting and cardiac standstill when swallowing. The attacks could be reproduced by artificial distention of the esophagus and prevented by atropine. Similar attacks may occur in patients with disease of the biliary tract.[52] Correll and Lindert[31a] described a case of Adams-Stokes syndrome due to a carotid sinus vagovagal reflex secondary to an esophageal diverticulum. In this instance digitalis was considered to be a contributing factor. Glossopharyngeal neuralgia, occurring with swallowing or talking, was associated in one case with bradycardia, cardiac arrest and syncope due to a carotid sinus reflex in which the glossopharyngeal nerve was the afferent arc.[133] Intracranial section of the glossopharyngeal nerve on the affected side relieved the neuralgia and abolished the paroxysms of cardiac arrest and syncope.

2. Postural Syncope and Chronic Orthostatic Hypotension. Prolonged standing in a fixed position may result in syncope, even in the normal person. Arising from bed after a prolonged illness often causes faintness or syncope. Cardiac asystole and syncope may occur following an episode of strenuous physical exertion.[47, 41] In these instances syncope is probably due to pooling of blood in the vessels of the lower extremities, which is ordinarily prevented by strong muscle tone, by the pumping action of the muscles which aid the venous return to the heart, and by normal vasoconstrictor adjustments which occur when the body assumes the erect position.

Chronic orthostatic hypotension,[46] or postural hypotension,[18] is a syndrome characterized by an extreme fall in blood pressure, dizziness and syncope, as soon as the patient attempts motionless standing. Except in the cases of postural hypotension temporarily following sympathectomy for hypertension, the pulse is usually unchanged during syncope but orthostatic tachycardia, auricular fibrillation and ST segment depression in the electrocardiogram have been described.[171a] The premonitory nausea and other symptoms preceding vasovagal syncope do not occur with this type of syncope. The fall in blood pressure results from a deficiency in the arterial vasoconstrictor mechanisms normally invoked with assumption of the erect position.[6] But Hickam[79] showed that a large fall in cardiac output, as well as failure of compensatory arterial constriction, is a factor in the postural reduction in blood pressure in certain cases of orthostatic hypotension. Orthostatic hypotension has also been attributed to a deficient venous return due to an abnormally low venous-capillary tone with consequent pooling of blood in the dependent parts.[171a]

Chronic orthostatic hypotension is probably due to serious underlying disease of the central nervous system.[43] It is observed in patients with tabes dorsalis, syringomyelia, Addison's disease and Simmonds' disease.[148] Postural hypotension is a temporary sequel of sympathectomy for hypotension. In some cases of idiopathic postural hypotension there is an absence of sweating which sug-

gests a disturbance in sympathetic innervation[149] (asympathicotonic hypotension).[119] East and Brigden[39] described a triad of anhydrosis, postural hypotension and impotence, occurring in middle-aged males. The underlying pathologic lesion in chronic postural hypotension is probably in the hypothalamus where the sweating center and a subcortical vasomotor center are situated.

3. Cardiac Syncope. This type is characterized by sudden loss of consciousness, with slight or no premonitory symptoms. It is due to cerebral anemia caused by ventricular asystole. The underlying causes are either (a) heart block with Adams-Stokes syndrome (p. 302), (b) disorders of the heart beat, such as sinoauricular standstill or sinoauricular block (p. 242), or paroxysmal auricular fibrillation[29] and (c) calcific aortic stenosis. Cardiac arrest occurs because of failure of the ventricular pacemaker in cases of heart block or because of ventricular asystole due to carotid sinus and vagal reflexes. The syncope of the Adams-Stokes syndrome may be due to either ventricular standstill or fibrillation (p. 287). The syncope of aortic stenosis is usually due to relative cerebral ischemia on exertion, but may be caused by reflex cardiac standstill through the carotid sinus or by heart block with ventricular arrest.

4. Anoxic Syncope. This includes cases of syncope occurring in high altitudes, syncope with extreme exertion, or syncope on exertion in patients with underlying congenital heart disease, aortic stenosis or decompensated chronic pulmonary disease.

5. Other Types of Syncope. Under this heading may be included cases of syncope due to severe head injuries, to severe local vascular disease of the brain, to drug sensitivity (e.g., after procaine injection), to hypoglycemia caused by insulin shock or an Addisonian crisis.

6. Hysterical fainting is a special type of loss of consciousness of profound psychologic origin. It occurs without alteration of pulse or blood pressure and without electroencephalographic abnormalities.[135]

Aviation and Syncope

Syncope presents an important problem in flying, especially for pilots. In a study of 500 cases of syncope involving pilots and air crew, 42 per cent were interpreted as primarily of emotional origin, 24 per cent as primarily neurogenic, 31 per cent as primarily cardiovascular and 3 per cent unclassified.[137] Hyperventilation of emotional origin was a frequent factor in the production of convulsions.

Directly associated with aviation are the cases of syncope due to cerebral anoxia, induced by low atmospheric pressure[136] when flying at great heights, or by positive acceleration in the long axis of the body (blackout), or when the plane decelerates during ascent from a sharp dive at maximum acceleration. During rapid ascent of a plane, decompression with release of nitrogen and other gaseous bubbles from solution in the blood may cause aeroembolism with cerebral vascular occlusion and possible syncope or death.

Differential diagnosis of the various types of syncope can usually be made by a very detailed history of the events and symptoms preceding, during and after the attack, by a careful examination and sometimes by special tests (carotid sinus pressure, electrocardiography, electroencephalography, etc.), and by observing the effects of drugs. An excellent discussion may be found in the article by G. L. Engel.[46]

Treatment of Syncope

A recumbent or head-down position abolishes most attacks of syncope.

In the cases of frequent syncopal attacks (postural hypotension), the cause should be treated if possible (large varicose veins, Addison's disease). Leg bandages and abdominal binders may be employed to help the venous return. Training the patient with a head-up bed, 20° above horizontal, has been recommended in the treatment of chronic postural hypotension.[82, 103] The most effective treatment is the continued administration of the sympathomimetic (vasoconstricting) drugs.

Ephedrine sulphate, 25 mg., or amphetamine, 5 to 10 mg.,[93, 36] may be given orally one to four times daily, especially in the earlier part of the day. Paredrine hydrobromide has a more sustained action and less central effects and may be given orally in 60 mg. doses three times daily.[115] Sometimes it is more effective to give a single daily dose of 100 to 160 mg. of paredrine one-half hour to an hour before arising.[171a] Similar advantages apply to neosynephrine which has been found effective in 20 mg. doses three times daily (following larger initial doses) after ephedrine and amphetamine had failed to control the syncopal attacks. Paredrine and neosynephrine may be used parenterally to control the syncope of spinal anesthesia (p. 224). It may be necessary to combine the sympathomimetic drugs with mild sedatives to counteract nervous excitation or sleeplessness.

The sympathomimetic drugs are also used in cases of syncope due to a hypersensitive carotid sinus syndrome. In addition, tincture of belladonna, 10 to 15 minims three times daily, or atropine sulfate, 0.3 mg. ($\frac{1}{200}$ grain) three times daily, may be helpful. In some instances surgical denervation of the carotid sinus (after a preliminary therapeutic test with procaine infiltration) may be advisable to eliminate the attacks.[24, 96] The use of epinephrine and other sympathomimetic drugs in syncope of Adams-Stokes syndrome is discussed elsewhere (p. 305). Syncope due to procaine sensitivity should be treated with barbiturates and not with sympathomimetic agents. The management of cardiac arrest under anesthesia has been discussed by Ruzicka and Nicholson.[141]

SUDDEN DEATH

Sudden death denotes the *quick* and *unexpected* termination of life.[73] This may include death instantaneously or within a few minutes,[163] sudden syncope with deepening and fatal coma, or an acute illness without unconsciousness which is unexpectedly fatal within twenty-four hours.[111]

Pathologic Physiology

Sudden death results from sudden, irreversible and intense cerebral anoxia. The responsible mechanisms are similar to those causing syncope or shock but more rapid and more severe, and therefore irreversible.

These mechanisms include (a) sudden local, traumatic, toxic, vascular or metabolic injury to the brain, (b) exsanguinating hemorrhage with medullary anoxia or pericardial hemorrhage causing cardiac tamponade, (c) massive pulmonary embolism with obstruction of blood flow and cerebral anoxia, (d) ventricular asystole.

The last group is of special interest to the cardiologist. Often in instances of sudden death postmortem examinations fail to reveal the cause. Coronary

arteriosclerosis or other cardiac disease is frequent, but insufficient in degree to explain the sudden end.[163, 100, 97] It is believed that death in such cases is due to a physiologic disturbance resulting in cessation of the heart beat. Cessation of the heart beat may be due to cardiac standstill or to ventricular fibrillation.[151]

Belief in the causal relationship of ventricular fibrillation to sudden death is based on (a) observations of this arrhythmia prior to death of experimental animals, especially following coronary artery ligation,[104, 76] and (b) its presence in electrocardiographic tracings taken by chance in patients who died during the recording.[67, 154] On the other hand Weiss[163] stressed the possible relation of cardiac standstill (caused by carotid sinus and vagal reflexes or heart block) to sudden death. Cardiac standstill is sometimes observed in exposed hearts when sudden death occurs during operation. In a recent study of terminal electrocardiograms Stroud and Feil[151] found that sudden death was associated as often with cardiac standstill as with ventricular fibrillation. In the presence of coronary or cardiac disease, the myocardium is especially susceptible to both of these forms of sudden death.

Etiology and Pathology

Cases of sudden death are usually seen by the coroner. A physician, summoned to see an individual who died suddenly, must be cautious in excluding factors of violence and poisoning, even when there is no overt evidence and even when the individual was known to have some competent producing cause. No death certificate should be issued without the approval of the coroner or official medical examiner if the physician was not in attendance at the time of death or if there is a claim of trauma as the cause of death.

Excluding deaths due to trauma or poisoning, the commonest causes of sudden death[73, 78, 112, 132] are (1) diseases of the heart and aorta, (2) respiratory diseases especially pneumonia, (3) cerebral complications, especially those associated with hemorrhage, (4) diseases of the digestive and urinary tracts.

Among the precipitating causes are severe exertion,[84] especially in warm weather, straining at stool, anesthesia, aspiration of body cavities, fright, and other powerful emotions.

Heart disease is by far the commonest cause of sudden death and coronary arteriosclerosis accounts for at least 60 to 80 per cent of these sudden cardiac deaths.[51, 113] Attention has recently been drawn to the frequency of sudden death in young men with advanced coronary arteriosclerosis but without coronary occlusion or myocardial infarction.[114, 61, 112, 171] But sudden death may result at the onset of an acute coronary occlusion or from ventricular rupture following myocardial infarction. Massive pulmonary embolism is a common cause of death in patients with acute myocardial infarction as well as in patients bedridden for other reasons.

Calcific aortic stenosis is the commonest valvular lesion associated with sudden death, but the latter may occur with any other valvular or myocardial disease.

Sudden death occurs more often with syphilitic than with rheumatic aortic insufficiency, probably because of the accompanying ostial stenosis in the former. Sudden death in syphilitic aortitis[95] may also be due to rupture of an aortic aneurysm.

Among natural causes of sudden death to be remembered are acute respiratory infections and congenital heart disease in infants; coronary arteriosclerosis, rupture of a congenital cerebral aneurysm, tubal rupture in ectopic pregnancy, brain tumor and fulminating meningitis in young adults; coronary artery disease and syphilitic aortitis, dissecting aneurysm of the aorta and acute gastrointestinal bleeding in middle age and beyond.

Prevention and Treatment

Maintenance doses of quinidine in cardiac patients have been recommended to avoid sudden death from ventricular fibrillation,[115] and promising results have been reported by Borg.[17] Similarly the administration of atropine has been suggested in anoxemic emergencies to prevent cardiac standstill. Cardiac massage and artificial respiration may restore the heart beat even after prolonged arrest (twenty to forty minutes) during an operation.[2, 154b] Treatment of ventricular fibrillation is discussed on p. 287.

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PART II

THE CARDIAC ARRHYTHMIAS

11

DISTURBANCES IN IMPULSE FORMATION

THE NORMAL FORMATION AND CONDUCTION OF IMPULSES

The heart possesses within itself the quality of automatic, rhythmic contraction. The ability to initiate and to conduct the impulses exciting muscular contraction resides in specialized neuromuscular tissue known as the conduction system. The latter is located on the endocardial surface and is composed of the sinoauricular node (of Keith and Flack),[45] the auriculoventricular node (of Tawara),[80] the auriculoventricular bundle (of His),[40] the bundle branches and the Purkinje fibers. A Purkinje conduction network has also been described within the myocardium of the mammalian ventricle,[2] but this is uncertain.

Normally the heart beat is controlled by rhythmic impulses arising in the sinoauricular node, which is therefore termed the *pacemaker of the heart*.[53] The *sinoauricular node* is a club-shaped or comma-shaped mass about 2.5 cm. long and 2 to 5 mm. wide lying in the sulcus terminalis, a groove between the junction of the opening of the superior vena cava and the right auricular appendage. From the sinoauricular (s-a) node the impulse spreads throughout both atria, activating the right about 0.01 second before the left, incidentally reaching the auriculoventricular (a-v) node. There is uncertainty as to the existence of specialized conduction pathways between the s-a and a-v nodes and between the left and right atria.

The *auriculoventricular node* is a structure about 5 mm. long and 2 to 3 mm. wide, located posteriorly on the right side of the interauricular septum, slightly below and anterior to the opening of the coronary sinus. Its upper end sends fan-like branches toward the coronary sinus, and its lower portion is continuous with the bundle of His. The *bundle of His* (*a-v bundle*) which conducts the impulse from the a-v node forms the connecting link between the atria and ventricles. It is a compact cord of tissue about 2 cm. long, on the right side of the interauricular septum and atop the interventricular septum, where it divides into two main branches. A striking characteristic of the a-v node (and bundle) is the retardation of the impulse for 0.05 to 0.06 second, during which time auricular contraction is completed before the ventricles are excited.

The a-v bundle, on reaching the membranous portion of the interventricular septum (undefended space), bifurcates into two branches (bundle branches) along which the cardiac impulse courses on either side of the septum. Each

bundle branch, on approaching the apex, ramifies profusely and spreads subendocardially to form a widespread syncytial network (fibers of Purkinje).[66] The impulse (excitation wave) passes from the left and right bundle branches to the subendocardial fibers of Purkinje, to activate the left and right ventricles respectively. Having reached the subendocardium, the impulse extends perpendicularly to the subpericardial myocardium. (For studies on the development and propagation of the cardiac impulse, see Lewis et al.[52] and Abramson and Jochim).[1]

This classic description of the conduction system has been challenged by Glomset and associates[33] who were unable to find the definite anatomic structures mentioned above. Their heretical observations have not been confirmed.

NERVOUS CONTROL OF THE HEART BEAT

The inherent automatism of the heart may be modified by the autonomic nervous system, of which the sympathetic component supplies the atria and ventricles, and the parasympathetic (the vagus) supplies only the atria (especially the sinoauricular and the auriculoventricular nodes).

Various visceral and peripheral afferent nerves transmit impulses to the cardiac centers in the medulla from which efferent vagal fibers to the auricular nodes and bundle of His may cause slowing of the heart beat and prolongation of the auriculoventricular conduction time.[47] There is evidence that the right vagus nerve is usually the major factor in slowing the cardiac rate while the left vagus is more effective in depressing a-v conduction.[30] The vagi also reduce the irritability and the refractory period of the auricular musculature, an action which is important in auricular fibrillation and flutter (p. 272). The carotid sinus (p. 9) is an especially important nerve terminus, by way of which vagal reflexes are mediated.[39]

Similarly visceral and peripheral afferent impulses to the cardiac medullary center may stimulate afferent sympathetic fibers to the heart and increase the cardiac rate.[11] Impulses from higher cerebral centers (emotional states) as well as chemical substances (epinephrine) may also stimulate the sympathetic (accelerator) nerves. In some animals, at least, there is evidence that the right accelerator nerve excites the sinoauricular node predominantly and thereby increases the heart rate, while the left enhances the rhythmicity of the auriculoventricular node, which may even assume the role of pacemaker of the heart (p. 243). Among sympathetic reflexes, the Bainbridge reflex (p. 9) (distention of the venae cavae and right atrium causing cardiac acceleration) is especially important in circulatory physiology. Normally tonic impulses travel to the heart along both sympathetic and vagal fibers and undergo frequent physiologic changes in intensity.[70]

CLASSIFICATION OF DISORDERS OF THE HEART BEAT

In general, cardiac arrhythmias result from disturbances in impulse formation or impulse conduction, and these may be further subdivided as follows:

I. Disturbances in impulse formation.
  A. Sinoauricular (sinus) rhythms (nomotopic rhythm).
    1. With abnormal rate
      a. Sinus tachycardia
      b. Sinus bradycardia

2. With irregular sequence of impulse formation
   a. Sinus arrhythmia
   b. Sinus arrest and auricular standstill

B. Ectopic rhythms (heterotopic rhythms).
   1. Escape rhythms (nodal rhythm and idioventricular rhythm)
   2. Premature contractions (extrasystoles)
   3. Paroxysmal tachycardia
   4. Auricular flutter
   5. Auricular fibrillation
   6. Ventricular tachycardia
   7. Ventricular fibrillation

II. Disturbances in conduction of the cardiac impulse.
   A. Sinoauricular heart block.
   B. Auriculoventricular heart block (partial and complete).
   C. Bundle branch block.
   D. Short P-R interval with prolonged QRS. (WPW)

The above classification is based on the physiologic disturbances in the initiation and propagation of the cardiac impulse. It is useful in the understanding of the associated electrocardiographic abnormalities. From the practical viewpoint of bedside diagnosis, it is simpler to observe whether the cardiac rhythm is regular or irregular, and whether the rate is unusually rapid (tachycardia), unusually slow (bradycardia) or normal.

Tachycardias which are regular include: (1) sinoauricular (sinus) tachycardia, (2) paroxysmal auricular tachycardia, (3) ventricular tachycardia and (4) most instances of auricular flutter. Irregular tachycardias include: (1) auricular fibrillation and (2) sinus tachycardia with numerous premature beats.

Bradycardias with regular rhythm include: (1) sinus bradycardia, (2) nodal rhythm, (3) severe partial heart block with constant degree of block and (4) complete heart block. Irregular bradycardias include: (1) sinoauricular bradycardia with marked sinus arrhythmia or frequent premature beats, and (2) partial heart block with frequent dropped beats or changing degree of block.

Irregular rhythms with normal heart rate include frequent premature beats, auricular fibrillation with ventricular rate slowed by digitalis, sinus arrhythmia and partial heart block with dropped beats.

SINUS TACHYCARDIA

The normal heart rate of adults at rest varies between 60 and 90 per minute while that of infants ranges between 100 and 150. Sinus tachycardia denotes that the cardiac impulse arises normally in the sinoauricular node, but that the rate is increased above 90 to 100 per minute (adults). Knowledge of the individual's normal heart rate under given conditions is a better basis for determining the existence of tachycardia than arbitrary levels. Ordinarily the heart rate in sinus tachycardia does not exceed 160 per minute, a feature distinguishing it from that of paroxysmal auricular or ventricular tachycardia.

The *electrocardiogram* is characterized by abbreviation of the P-P intervals below 0.6 second and by recurrence of the P waves at regular intervals, each followed by a QRS complex. Occasionally, when the rate exceeds 150 per minute, the P waves may become fused with the preceding T wave. The reduction in the cardiac cycle is chiefly at the expense of the diastolic period. <0.6

Vagal depression and accelerator stimulation in varied degree account for sinus tachycardia.

Physiologic sinus tachycardia results from emotion, exercise, digestion, and other causes. Voluntary acceleration of the heart rate has been observed.[25] Certain drugs such as atropine and amyl nitrite may be used clinically to produce sinus tachycardia. Among pathologic conditions associated with sinus tachycardia are fever, hyperthyroidism, anemia, acute hemorrhage, shock, congestive heart failure and cardiac neurosis.

Examination of the heart and pulse discloses a regular rhythm with a rate exceeding 90 to 100 per minute. Differentiation from other tachycardias with *regular* rhythm may be made from the electrocardiogram or surmised on clinical grounds (p. 288). There may be no subjective symptoms, or there may be disagreeable palpitation, fatigue and breathlessness as in other tachycardias (p. 260).

The clinical significance depends on the basic cause. The tachycardia subsides when the underlying cause is removed. Sometimes tachycardia is noted without apparent cause. An unsuspected hyperthyroidism or anemia may be responsible and the possibility of their presence should be investigated. Occasionally a persistent sinus tachycardia disappears only after the elimination of tobacco, alcohol or excessive coffee.

SINUS BRADYCARDIA

Sinus bradycardia denotes that the cardiac impulse arises normally in the sinoauricular node, but that the cardiac rate is less than 60 per minute.

The *electrocardiogram* is characterized by prolongation of the P-P interval to 1 second or more, but the P waves recur regularly and are each followed by QRS complexes. Occasionally in bradycardias of vagal origin sinus arrhythmia (see below) is associated, and the P-P intervals are somewhat irregular. The P-R interval tends to be prolonged in sinus bradycardia. Slowing of the heart rate involves predominantly an elongation of diastole (T-P interval).

The *mechanism* is probably an increase of vagal tone or a diminution of sympathetic tone or both.

Normally, heart rates of 50 per minute or less are sometimes observed during sleep and are not uncommon during pregnancy. Sinus bradycardia is fairly common among those engaged in strenuous labor and among trained athletes. Rates as low as 36 to 40 per minute have been observed in distance runners with normal hearts. Under pathologic circumstances sinus bradycardia may be associated with cerebral lesions, with increased intracranial pressure, coronary artery disease (occasionally), convalescence from infectious disease, myxedema, and icterus.

There are usually no clinical symptoms of sinus bradycardia, but dizziness, faintness or syncope may be associated with extremely slow cardiac rates. Syncopal attacks may be due to cardiac asystole.[63]

Examination of the heart and pulse discloses a regular rhythm with slowing of the heart rate below 60 per minute.

Sinus bradycardia must be differentiated from a slow nodal rhythm and from heart block. The presence of the normal systolic collapse in the jugular vein and the absence of jugular pulsations during the long diastolic pause may be distinctive. In heart block, auricular pulsations may be visible in the cervical veins and auricular cardiac sounds may be audible during the pauses between heart

beats. The electrocardiogram is usually necessary for a definite diagnosis. Sinus bradycardia may be indistinguishable from prolonged sinoauricular block with 2 : 1 rhythm (p. 294).

SINUS ARRHYTHMIA (PHASIC ARRHYTHMIA, JUVENILE ARRHYTHMIA)

The cardiac impulses arise normally in the sinoauricular node, but their rhythmicity varies. This gives rise to alternating periods of slower and more rapid cardiac rates. The variations are usually but not always related to respiration, the heart rate increasing with inspiration and diminishing with expiration (respiratory arrhythmia).

The *electrocardiogram* discloses P waves, each followed by QRS complexes in normal succession, but the P-P intervals form alternate series of shorter and longer cycles. The changes in length are virtually confined to the T-P interval (Fig. 24). The configuration of the P wave may show slight alterations, suggesting shifting sites of origin of the cardiac impulse, but all within the sinoauricular node. The P-R interval may be slightly shorter during the more rapid rates than during the slower cycles.

Mechanism. Careful analysis of electrocardiograms with normal sinus rhythm and rates under 80 per minute discloses that there is no absolute regularity and

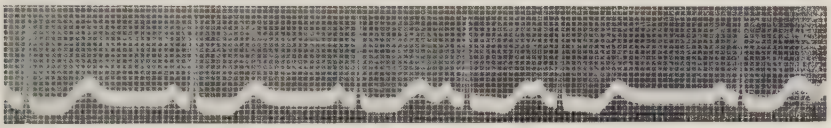


Fig. 24. Sinus arrhythmia. A woman, aged 28, with diabetic acidosis but without heart disease. Lead III. Progressive decrease, then increase in length of cardiac cycles. Effect chiefly on length of T-P interval.

that cycle lengths vary slightly but definitely. This is probably due to physiologic phasic variations in the vagal (and sympathetic?) tonus. Sinus arrhythmia is merely an exaggeration of this normal tendency. Impulses from the respiratory center and lungs at the height of inspiration depress the vagus center and accelerate the cardiac rate. Sinus arrhythmia is commonest in hearts with bradycardia, presumably because there the vagal influence tends to be maximal. Sinus arrhythmia may be associated with other influences which affect vagal tonus, independently of the respiratory phases.

Sinus arrhythmia occurs commonly among children and among the aged.[24] It is often observed during convalescence from infectious diseases, following digitalization, and in diseases of the brain with increased intracranial tension, all conditions associated with vagal stimulation or increased vagal tonus.

Clinically, sinus arrhythmia is recognizable by the fairly regular alternation of several rapid heart or pulse beats with a similar cycle of slower beats. The relation of the rapid beats to inspiration and the slow beats to expiration is diagnostic. Intensification of the arrhythmia by deep breathing, or its abolition by breath-holding or by exercise, may also be helpful in diagnosis. Rarely an electrocardiogram is required to distinguish with certainty sinus arrhythmia from auricular fibrillation with slow ventricular rate.

As a rule sinus arrhythmia is of no clinical importance and requires no treatment. When accompanied by intense bradycardia, it may be associated with attacks of dizziness. When sinus arrhythmia results from vagal stimulation

secondary to serious cerebral disease, or the like, the outlook is that of the underlying disease.

SINUS ARREST AND AURICULAR STANDSTILL

Sinus arrest (sinoauricular standstill or sinus pause) denotes a pause in the cardiac rhythm due to a momentary failure of the sinus node to initiate an impulse.

The *electrocardiogram* is characterized by a prolonged diastolic pause between two PQRST complexes which are entirely normal (Fig. 25). The pause is not an exact multiple of the normal P-P cycle.

The *mechanism* is probably a reflex vagal stimulation through the carotid sinus or a direct stimulation of the vagal center.

Sinus arrest may occur after gagging or stimulation of the pharynx. It may be observed in patients with an hypersensitive carotid sinus. Sinus arrest and sinus arrhythmia are sometimes associated, both resulting from conditions which stimulate the vagus nerve.

Sinus arrest is usually of no clinical significance, but if the pause is sufficiently long, dizziness, faintness or even syncope may ensue.

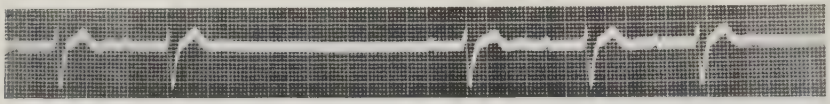


Fig. 25. Sinus arrest or sinus inertia. A man, aged 73, with coronary artery disease. Lead II. Pauses without atrial or ventricular contraction. Sinoauricular block not excluded but less probable because pauses are not multiples of normal P-P interval. There are associated conduction disturbances.

Clinically, sinus arrest is recognized by the omission of a beat (dropped beat), at the cardiac apex as well as at the wrist. Sinus arrest may be indistinguishable from sinoauricular block (p. 293). It must be differentiated from the pause of dropped beats in partial heart block (p. 296) and the compensatory pause following an early premature beat.

Auricular standstill denotes a pause in auricular contraction, while the ventricle contracts in response to stimulation by its own pacemaker.[69] Auricular standstill is secondary either to sinus arrest or sinoauricular block.[12] Recently Magnasson[57] reported 3 cases of his own and 31 cases collected from the literature.

The *electrocardiogram* shows a regular sequence of ventricular complexes, but one or more P waves are absent. Bradycardia is commonly associated.

Mechanism. When the sinoauricular node fails to initiate an impulse, or the impulse is blocked from reaching the atrium, there is no auricular contraction. However, a pacemaker of lower rhythmicity (p. 243), situated in the bundle or ventricle, activates the ventricle and causes contraction.

The *cause* of auricular standstill is usually digitalis or quinidine intoxication, but organic heart disease is often present.

Clinically, the rhythm is regular, but there may be intense slowing of the heart. An electrocardiogram is essential for diagnosis. When auricular standstill is due to digitalis or quinidine, these drugs should be stopped and, if necessary, resumed later in smaller dosage.

ECTOPIC BEATS AND ECTOPIC RHYTHMS

All parts of the conduction system possess the property of rhythmicity, that is, of initiating impulses and exciting contraction. But the degree of rhythmicity, i.e., the rapidity with which impulses are formed and released, varies. Normally the sinoauricular node has the greatest rhythmicity and dominates the rhythm of the heart. It is therefore termed the pacemaker. Lesser degrees of rhythmicity are possessed by the auriculoventricular node, the a-v bundle and the ventricular specialized tissue, in that order. Thus while the s-a node emits impulses at 70 to 80 per minute, the a-v node initiates them at 40 to 60 per minute, and the bundle and lower centers at less than 40 per minute. The impulses released by these other centers are nullified by the more frequent sinus impulses. However, when the rhythmicity of the sinoauricular node is depressed or the rhythmicity of some other center of the heart is enhanced above that of the sinus node, the lower center may control the heart rhythm and become the pacemaker. Whenever isolated cardiac beats are excited by some center other than the sinus node, they are termed ectopic beats. When a more continuous rhythm is initiated by a focus outside the sinus node, it is termed an ectopic rhythm.

Escape Rhythm

Escape rhythms are those initiated by lower centers when the sinoauricular node fails to initiate impulses, when its rhythmicity is depressed, or when its impulses are completely blocked. When the a-v node becomes the pacemaker for a single beat, it is termed a nodal escaped beat; when it becomes pacemaker for a continuous period, nodal rhythm appears. If the s-a node and a-v node are sufficiently depressed or fail to initiate impulses, a focus in the bundle or ventricles controls ventricular contraction either for isolated beats (ventricular escape) or for a continuous rhythm termed idioventricular rhythm.

Auriculoventricular (Nodal) Rhythm. Experimentally, nodal rhythm can be produced by cooling, clamping or chemical destruction of the sinoauricular node,[23, 42] and occasionally by vagal stimulation. The rhythm of a lower center thus released represents an escape rhythm, and the cardiac rate is slow, averaging 40 to 60 per minute.[29] But nodal rhythm may be associated with a normal rate and a-v nodal tachycardia has also been described.

Occasionally, isolated beats are controlled by the a-v node while others are controlled in their normal fashion by the sinoauricular node. This phenomenon is termed wandering or shifting pacemaker. Such shifts in pacemaker occur whenever the rates of impulse formation in the sinoauricular and atrioventricular nodes are almost identical. Then slight, physiologic changes in vagal tonus may modify these rates of impulse formation sufficiently to permit one or the other of the nodal centers to gain control of the heart rate.[15, 32] Pressure on the carotid sinus or eyeball (oculovagal reflex) may induce transient a-v beats or rhythm interspersed among stretches of sinus rhythm. Occasionally the slight variation in vagal tonus caused by sitting up from the recumbent position may result in transient nodal rhythm.[41] Other beats or rhythms dominated by the a-v node are nodal premature beats (p. 251) or nodal tachycardia (p. 261). These represent enhancement of nodal rhythmicity rather than primary depression of the sinus node, but both may coexist.

The Electrocardiogram. With *isolated nodal escape beats* there is a sinus

pause followed by a normal QRS complex, while the P wave is usually inverted and either precedes, fuses with or follows the QRS complex. The P wave is usually altered in configuration because the origin of the auricular activation wave in the a-v node and its course differ from the normal. As a rule, the s-a node resumes its role as pacemaker after isolated nodal escape beats.

With continued a-v nodal control (*nodal rhythm*) the QRS complexes are normal and follow in regular sequence at a rate of 40 to 50 per minute. This denotes that the cardiac impulse follows its normal course in depolarizing the ventricles. On the other hand, the a-v nodal impulse must be conducted retrograde toward the s-a node and atria in activating these chambers. This modifies both the position and configuration of the P waves. It is assumed that when the cardiac impulse arises in the head or coronary sinus portion of the a-v node (coronary sinus rhythm),[78] auricular depolarization precedes that of the ventricles and the P wave precedes the QRS; when it arises in the body or midportion, both atria and ventricles are simultaneously activated and the P wave is lost in the QRS; when the impulse arises in the tail of the a-v node, it reaches the ventricles prior to the atria, and the QRS precedes the P wave. But even when the P wave in nodal rhythm precedes the QRS as it does normally, the P-R interval is shortened (0.11 second or less) because the distance traversed by the impulse from the a-v node to the ventricles is always shorter than from the sinus node. The retrograde direction of the a-v nodal impulse as it activates the atria causes an inversion of the P wave in leads II and III (Fig. 26A). The effect on lead I depends on whether the depolarizing process runs from right to left as normally or is altered; accordingly, P_1 may be upright, diphasic or inverted.

Rarely a-v nodal rhythm is coupled with premature contractions of sinoauricular, auricular or ventricular origin.[64]

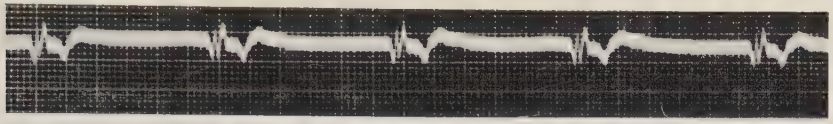
Clinically, nodal rhythm is observed in conditions which depress the rate of impulse formation in the sinoauricular node or which prevent the sinus impulses from reaching and activating the atria (sinoauricular block). Usually underlying heart disease is present,[26] but physiologic or pathologic influences which increase vagal tone are contributory or precipitating factors in the initiation of a-v rhythm. Hypertension and coronary artery disease are commonly found in cases of coronary sinus rhythm.[78] A-v rhythm has been attributed to the impairment of the blood supply to the sinoauricular node, especially in elderly persons with high vagal tonus. In such persons deep breathing, digitalis or anesthesia may induce a-v (nodal) rhythm. Nodal rhythm has been observed in association with acute coronary occlusion,[59] in various infectious diseases,[19] especially active rheumatic fever,[15] and after auricular flutter. But a-v nodal rhythm also occurs in apparently normal hearts, both as a result of vagal stimulation by carotid sinus or ocular pressure[43, 34, 28] and paradoxically after the parenteral administration of atropine.[28, 84, 21] A-v nodal rhythm has also been observed after the administration of digitalis[67] and quinidine.[36]

Despite this variety of circumstances under which it may develop, actually a-v rhythm occurs relatively infrequently. It is almost always a transient phenomenon alternating with sinus rhythm. Usually a-v rhythm persists for brief runs, but occasionally it may persist for several days or weeks.

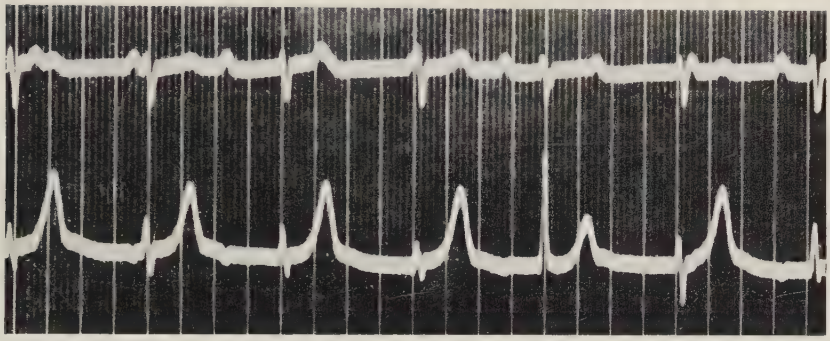
Clinical symptoms are uncommon and rarely distressing. But there may be disturbing palpitation or a choking sensation or fullness in the neck due to simultaneous ventricular and auricular contraction. The latter forces the auric-

ular contents into the cervical veins as the tricuspid valve is shut. For this reason also there may be an intensification of the first cardiac sound and there may be a prominent pulsation in the cervical veins due to the abnormal amplitude of the auricular ("a") wave.

Diagnosis usually requires electrocardiographic study (p. 244) but a-v rhythm may be suspected from the bradycardia and from the auricular systolic regurgitation waves in the cervical veins. Bradycardia due to heart block may be distinguished by the presence of auricular waves in the long diastolic intervals between beats.



A



B

Fig. 26. *A*, Nodal rhythm. A man, aged 56, with healed anterior wall infarction. Lead II. Inverted P waves following ventricular deflection.

B, A-v dissociation with interference beats. Leads III and IV taken simultaneously. Atria responding to sinus and ventricles to a-v node at slightly different rates (a-v dissociation). P-R relationship constantly changing. After four ventricular responses to the a-v node, the ventricle responds to a sinus impulse (interference beat) and shows a different (normal) configuration.

Treatment either is unnecessary, is directed toward the underlying disease (e.g. coronary disease), or consists in removal of the causative agent (digitalis). Nodal rhythm can usually be abolished by atropine or exercise.

Auriculoventricular Rhythm with Reciprocal Beats. In most instances of a-v (nodal) rhythm, the nodal impulse activates the ventricles and also is transmitted retrograde to activate the atria. Occasionally this same retrograde nodal impulse, after effecting an auricular contraction, may retrace its path to the a-v node and continue through the bundle and bundle branches to induce another ventricular contraction.[83, 20] This additional contraction is termed a reciprocal beat and when many such beats occur there is a reciprocal or reciprocating rhythm.[17, 6]

Reciprocal beats occur as a rule in that type of a-v rhythm in which the ventricles contract before the atria and in which the atrial activation is so delayed that the ventricle is no longer refractory and can respond to the returning auricular (nodal) impulse. Often there is a progressive, increasing delay in

retrograde conduction until finally a reciprocal beat occurs, resembling a reversed Wenckebach period (p. 297). This delay in retrograde conduction of the a-v nodal impulse is usually induced by carotid sinus pressure or digitalis therapy.

The *electrocardiogram* shows the QRS complex of a-v rhythm followed by an abnormal (nodal) P wave after an interval which is longer than usual. This P wave is then followed rapidly by another QRS complex. The result is a succession of QRS complexes (ventricular beats) resembling bigemini or coupling (p. 248) ordinarily seen when a premature ventricular beat (extrasystole) follows a normal ventricular contraction.[41, 55] The term "return extrasystole" is sometimes applied to the reciprocal beat.

Auriculoventricular Rhythm and Auriculoventricular Dissociation. I have stated that in auriculoventricular rhythm the nodal impulse is usually conducted retrograde as well as forward and activates the atria as well as the ventricles. Sometimes, probably as a result of retrograde (unidirectional) auricular block, the nodal impulse activates the ventricles but not the atria.[79] In such cases the sinus node may continue to activate the atria while the a-v node controls only the ventricles in spite of the more rapid stimulus formation in the a-v as compared with the s-a node. This independence of auricular and ventricular contractions in response to different pacemakers is termed auriculoventricular dissociation. The ventricular rate, controlled by the a-v node, may exceed that of the atria which are responding to a depressed sinoauricular node. This type of a-v dissociation is usually the result of digitalis, or of infections such as rheumatic fever. Another form of a-v dissociation may result from complete auriculoventricular block in which neither sinus nor a-v nodal impulses reach the ventricles and the latter respond to a pacemaker in the bundle below the block (see idioventricular rhythm). Complete a-v block with dissociation is distinguished by more frequent auricular contractions than ventricular, while in the type under discussion the ventricular rate is more rapid than the auricular.

A-V Dissociation with Interference Beats (Interference Dissociation). In the cases of auriculoventricular rhythm and dissociation, an occasional sinus impulse may succeed in activating the ventricles as well as the atria despite the higher rate of impulse formation in the a-v node. The ventricular contraction in response to a sinus impulse interrupts the usual contractions in response to a-v nodal impulses and is termed an *interference beat.* The combination of interference beats with auriculoventricular dissociation is termed *interference dissociation*[61] (Fig. 26B).

Ordinarily in a-v rhythm with dissociation, the slow sinus impulses cannot activate the ventricles because the a-v node and lower conduction system are refractory when the sinus impulse arrives. Because of continuous although slight variations in the rate of formation of sinus impulses and similar variations in the time relationship of sinus and a-v nodal impulses, a sinus impulse occasionally arrives at the a-v node when the latter is not refractory, traverses the bundle and its branches and activates the similarly nonrefractory ventricles. The sinus ventricular beat follows the a-v nodal ventricular beat after an abnormally brief interval and gives the appearance of a coupled extrasystole (p. 248).

The *electrocardiogram* in interference dissociation is characterized by QRS complexes of normal configuration (a-v nodal origin) occurring independently of and at varying intervals from normal sinus P waves. The P wave may be lost in one (nodal) QRS and then follow successive (nodal) QRS complexes at

progressively longer intervals until it occurs so late that it is followed by a (sinus) QRS complex which occurs prematurely in response to the sinus impulse. The irregularity simulates premature auricular systoles. These interference beats are distinguished from reciprocal beats (p. 245) by the normal upright sinus P waves between the coupled QRS complexes.[38, 88] In reciprocal beats the premature QRS follows a returning a-v nodal impulse which is represented by a deformed or inverted P wave. Both accompany a-v nodal rhythm but reciprocal beats occur only if there is no complete retrograde auricular block to the a-v nodal impulse, while interference beats occur only in the presence of such a retrograde block which is responsible for the a-v dissociation. Both reciprocal and interference beats occur in a-v rhythm in which the ventricular rate is slightly more rapid than the auricular and which is usually the result of sinoauricular depression or sinoauricular block caused by digitalis or in acute infections such as rheumatic fever.

Idioventricular Rhythm. We have seen that depression of the rate of impulse formation in the sinoauricular node or block of sinoauricular impulses may permit the a-v node to become the pacemaker of the heart for isolated beats (nodal escape beats) or for continuous periods (a-v nodal rhythm). Similar depression of the a-v as well as the sinoauricular node (carotid sinus or ocular pressure) or a block of a-v conduction (digitalis, organic lesions) may permit still lower automatic centers in the main a-v bundle or in the specific tissue of one of the ventricles to assume control of the heart beat. When single ventricular impulses pace the heart, isolated ventricular escape beats are observed. When the lower center maintains more continuous control, there is idioventricular rhythm or ventricular automatism. The atria remain under sinoauricular control.

Idioventricular rhythm is observed most commonly in cases of auriculoventricular block (p. 297) in which impulses from the s-a or a-v node are prevented from reaching the ventricles. The pacemaker probably arises in the a-v bundle below the site of obstruction, for the configuration of the QRS is normal (supraventricular type), denoting a normal pathway of the wave of ventricular excitation. The ventricular rate is usually less than 40 per minute. Since the atria are independently activated by the sinus node, the P waves are of normal configuration and occur at rates of 70 to 80 per minute. Thus, as in some cases of a-v rhythm, idioventricular rhythm is accompanied by auriculoventricular dissociation. Since the ventricular complex in idioventricular rhythm is usually identical with that of a-v rhythm, the two conditions may be indistinguishable when there is a-v dissociation. The ventricular rate is usually more rapid (above 40) in a-v rhythm, there is usually a prolonged pause (preautomatic pause) before the onset of ventricular automatism, and carotid sinus pressure (vagal stimulation) usually slows the ventricular rate in a-v but not in idioventricular rhythm, since the vagus does not extend below the a-v node. Retrograde conduction to the atria rarely if ever occurs in idioventricular rhythm but is common in a-v rhythm. In the presence of such retrograde conduction, a-v rhythm is generally easily distinguishable by the presence of P waves, usually inverted in leads II and III at abnormally short distances preceding or following the QRS complex.

When the idioventricular pacemaker is situated below the bundle of His, the QRS complex has a bizarre configuration characterized by widening, slurring and notching while the T wave is often opposite in direction to the main QRS

deflection. This abnormal appearance denotes an abnormal origin and course of ventricular excitation (p. 238). The electrocardiographic appearance of the ventricular complex (QRST) is identical with that of an extrasystole (premature beat) but may be distinguished by its occurrence after a prolonged pause instead of prematurely. In both of these, the P wave is usually obscured; in bundle branch block, the QRST is also similar but follows a normal sinus P wave after a normal or slightly prolonged P-R interval.

Prolonged idioventricular rhythm, arising in a center in the ventricles below the main bundle, rarely occurs in humans as an escape rhythm. On the other hand, ventricular foci may gain control of the heart as a result of factors which so increase the irritability of the ventricular conduction tissue that its rate of impulse formation exceeds that of the sinus or a-v nodes. The resulting rhythms are discussed under ventricular tachycardia–flutter–fibrillation.

Premature Beats

Premature beats or extrasystoles are cardiac contractions of ectopic origin which occur earlier than expected in the dominant or usual rhythm.[82, 14] The activating impulse may be in a ventricular focus (causing *ventricular premature beats*), or above the bifurcation of the bundle of His (causing *supraventricular premature beats*). Supraventricular premature beats may arise in the auriculoventricular node (nodal premature beats), elsewhere in the atria (auricular premature beats), or rarely in the "tail" of the s-a node instead of normally in its "head" (sinoauricular premature beats).[31]

Premature beats form the commonest of the cardiac arrhythmias and ventricular premature beats occur much more commonly than those arising in the a-v node or elsewhere in the atria.

The premature beats may occur irregularly and in isolated fashion or they may occur regularly with respect to each other and to the normal beats. When irregularities recur in regular fashion, they are termed allorhythms. When a normal beat followed by an extrasystole recurs seriatim, we term the rhythm *bigemini* or *coupling*. Coupling is induced by two beats in close proximity followed by a relatively longer "compensatory" pause. The commonest type of coupling is due to alternate extrasystoles and often caused by digitalis.[22, 27, 72a] Bigemini may also result from partial a-v block (p. 297), in which every third beat is dropped, from sinus pauses every third beat, and from 3:2 sinoauricular block (p. 294). (For a detailed discussion see Parsonnet et al.)[62] In similar fashion, trigemini denotes a grouping of beats in threes formed either by a normal beat and two successive premature beats, or by two normal beats followed by one premature beat. Similar rhythms may result from partial heart block in which every fourth beat is blocked, sinus pauses every fourth beat, and 4:3 sinoauricular block. It is essential that these rhythms be checked by listening at the apex of the heart, because premature beats may be too weak to produce a palpable pulse at the wrist.

Mechanism of Premature Beats. Premature beats are believed to arise when an ectopic focus in the heart becomes so irritable that its rate of impulse formation exceeds that of the sinus node. This concept explains the experimental production of extrasystoles by direct electrical, chemical, thermal or mechanical stimulation of local portions of the heart. Similar artificial stimuli have been utilized to evoke premature beats in the human heart exposed during operation.[4] Stimulation of the vagus and sympathetic nerves have induced extra-

systoles in dogs.[71, 50] There is also evidence that the higher centers such as the hypothalamus and possibly the cortex control the spinal sympathetic accelerator centers; stimulation of the posterior hypothalamus has elicited premature beats in cats.[9] Premature beats in animals observed during chloroform and other types of anesthesia are probably mediated through sympathetic nerves.[50] Certain drugs such as digitalis, epinephrine, ephedrine and barium chloride can evoke extrasystoles, probably directly by increasing neuromuscular irritability as well as indirectly by stimulating the autonomic nerves to the heart.

Several theories have been proposed to explain the exact mechanism by which extrasystoles arise:

1. One of these assumes that a single irritable focus in the heart muscle (or multiple foci) develops, emits rhythmic stimuli with greater frequency than the normal pacemaker, and occasionally, frequently or continuously gains domination of the cardiac rhythm.[37, 51] Whenever this new pacemaker can release an impulse which finds the heart muscle not refractory, it produces a premature beat.

2. The fact that premature beats often follow the preceding normal beat at exactly identical intervals suggests that the normal contraction in some way controls the ectopic beat which follows. De Boer[8] suggested the theory of reentry to explain this exact coupling. According to this concept the sinus impulse activates the heart and causes a cardiac contraction, then reenters the excitable ectopic focus of heart muscle by an aberrant pathway and elicits another contraction when the heart muscle is no longer refractory. The coupled extrasystole often occurs during the U wave of the preceding beat, at which time there is a supernormal phase of irritability which would favor the initiation of a premature beat. This might explain the constant time relationship between the extrasystole and preceding beat. According to experimental observations of de Boer[8] on the frog's heart, the mechanism responsible for premature beats, like that causing auricular flutter and fibrillation, is not that of rhythmic impulses from a punctate focus but the reentry of an impulse into a circus ring of muscle tissue (p. 272). This theory could explain the cases of bigemini due to ventricular premature beats, e.g., those due to digitalis intoxication, in which there is usually a fixed coupling in time relationship between normal and premature beats.[62]

3. A third theory based on the observations of Kaufmann and Rothberger[44] is that of *pararrhythmia*. According to their concept, abnormal beats (parasystoles) result from the interaction of two foci concurrently initiating impulses at different rates. As a rule, one of these is the normal pacemaker, the sinus node. The other or ectopic focus is responsible for an independent rhythm prevailing side by side (para) with the sinus rhythm. This ectopic site does not respond to the sinus impulse, but continues to form its own stimuli which effect a ventricular response whenever the ectopic stimulus falls outside of the refractory period. These rhythms work independently of each other and the sinus and parasystolic beats bear no constant time relationship to each other, unlike the two rhythms in interference dissociation (p. 246) or in many types of extrasystoles in which the sinus and ectopic beats are coupled at fixed intervals.

The parasystolic focus emits impulses which are characterized by absolute regularity, the cycles of which vary less than 0.01 second, in contrast with the sinus impulses which are more variable. In paroxysmal tachycardia (p. 261), which is explained by a similar mechanism, the absolute equality of cycles

between beats is apparent. But Kaufmann and Rothberger[44] also showed that if extrasystoles precede or follow a paroxysm of tachycardia, the interval between such isolated extrasystoles is a mathematically exact multiple of the interval between beats of the tachycardia. Of course many of the ectopic impulses are ineffective because of the refractory state of the muscle, which has just responded to a normal sinus impulse. Local blocks to the dominant sinus impulse (entrance block) are assumed to protect the ectopic center and its impulses from being inactivated.[76] Rarely the rate of impulse formation in the ectopic focus is more rapid than in the sinus node; in such instances some of the outgoing ectopic impulses are blocked from interfering with the sinus impulses (exit block).

It is probable that the premature beats or extrasystoles which are so termed on the basis of their clinical and electrocardiographic features are not all due to the same cause. In particular a distinction must be made between those extrasystoles which bear a fixed time relationship to the preceding beat and those which are independent of the basic rhythm. The former are probably released by an extraneous stimulus reaching an irritable focus rather than by stimuli originating independently at the ectopic focus.[77] Those extrasystoles



Fig. 27. Premature auricular beats. A woman, aged 47, without organic heart disease. Lead I. Second ventricular complex is a nodal extrasystole with inverted P following RS. Fourth ventricular complex is an auricular premature beat with a compensatory pause. Note coupling effect or bigemini.

which bear no constant time relationship to the sinus rhythm, but which recur with unchanging rhythm, are best explained by the theory of parasystole.

The Electrocardiogram in Premature Beats. The electrocardiogram differs with regard to auricular, auriculoventricular or nodal, and ventricular premature beats.

Auricular Premature Beats. An auricular complex and a ventricular complex occur earlier than anticipated (Fig. 27). The P wave is usually abnormal in conformation because the origin and course taken by the ectopic impulse are different from the normal. However, the P wave is always present although difficult at times to identify. When the ectopic impulse arises very close to the sinoauricular node or in its "tail," the P wave is similar in appearance to the normal P of the basic rhythm and its direction is the same in each lead as the normal P wave. When the ectopic impulse arises low in the atrium, its direction is usually retrograde toward the s-a node. In this circumstance P_2 and P_3 are inverted because the direction of the auricular depolarization process is opposite to the normal as it affects leads II and III. However, P_1 may be upright, isoelectric or inverted depending on the degree to which the ectopic impulse conforms to the normal right to left direction (of the sinus impulse). Sometimes premature beats briefly separated in time arise from different ectopic foci in the atria (multifocal auricular premature beats). This occurrence is betrayed by differences in form and direction of premature P waves in the same lead.

The *P-R interval* is usually greater than the minimal normal of 0.12 second

because the path of the ectopic impulse to the ventricle is at least as long as that of the normal sinus impulse. The P-R interval of the ectopic beat may be abnormally long if the ectopic center is very far from the sinoauricular node or if the premature beat occurs very early in the auricular refractory period before complete recovery from the preceding auricular contraction.

The QRST complex appears virtually normal, i. e., similar to the QRS of the basic rhythm in the same lead. For after the ectopic impulse has traversed the atrium, its course in the conduction system of the ventricle is identical with that of a normal sinus impulse. However, although the QRS of an auricular extrasystole resembles the normal, its amplitude is often altered and its conformation is slightly different (aberration of the QRS complex), perhaps due to a slight disturbance in bundle branch conduction or slight refractoriness of the ventricular muscle. Sometimes the QRS is so altered (slurred, notched and widened) that it resembles that of a ventricular premature beat. The height of the T wave may also be altered. The degree of prematurity of the atrial premature systole is probably the major factor determining the degree of aberration of the QRS.[5] Rarely also the ectopic auricular stimulus occurs so early that it cannot be transmitted through the a-v node and bundle, which are completely refractory, or it reaches a refractory ventricular muscle. Then the electrocardiogram of the auricular premature beat discloses an abnormal P wave without a following QRS complex.[68] This is termed a *blocked premature auricular beat.* It differs from heart block in that the P wave occurs prematurely and is usually different in configuration and direction from the P wave of the basic rhythm.

The QRST complex of an auricular premature beat is followed by a pause which is slightly longer than the basic T-P interval. This prolongation represents the normal interval between beats plus the interval consumed by the ectopic impulse to travel back to the sinoauricular node. If the P-P interval from the ectopic to the following normal beat is added to the P-P interval between the ectopic and preceding normal beat, it is somewhat less than 2 normal P-P intervals of the basic rhythm. Thus the T-P pause is longer than normal but not compensatory, i. e., it does not quite restore the dominant rhythm by exactly compensating for the abnormally short T-P interval before the premature beat.

(Auriculoventricular) Nodal or Junctional Premature Beats. The QRS complex occurs prematurely, but is usually normal in configuration (supraventricular type), since the nodal impulse follows the normal pathway as it activates the ventricles.

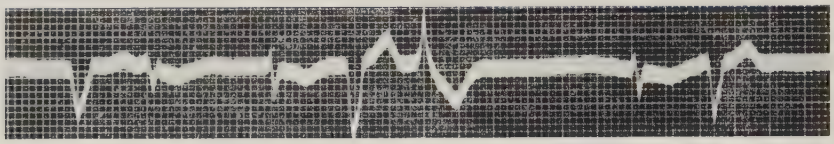
The origin of the premature beat in the a-v node or bundle is indicated by the abnormal position or configuration of the P wave (Fig. 27). The P wave represents either (a) retrograde activation of the atrium by the nodal impulse or (b) normal sinus activation of the atria while the nodal impulse activates the ventricles. In the former circumstance, the P wave is altered in configuration and either precedes, coincides with or follows the QRS. If the atria are activated by the sinus impulse, the P wave is normal in appearance, continues its basic rhythm and usually follows a QRS complex.

With retrograde conduction of the nodal impulse, the P-R interval is less than 0.12 second when it precedes the QRS complex, because the pathway from the a-v node to the ventricles is shorter than from the s-a node.

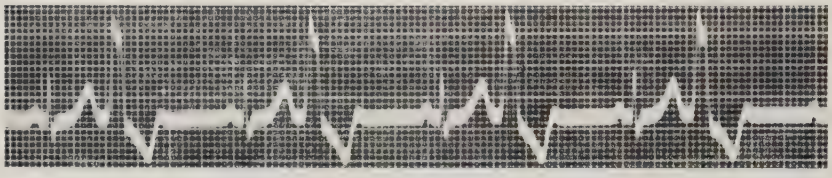
Ventricular Premature Beats. The *QRST complex* differs strikingly from

the normal because the ectopic impulse takes an abnormal and longer course through the ventricles (Fig. 28A). The QRS is of high voltage, slurred, notched and widened to 0.13 second or more. The T wave is altered secondarily. It is usually directed opposite to the QRS, and is wide and tall. Often the T wave is deformed by a P wave. The P wave, although present, is usually partially or completely obscured by the QRST complex.

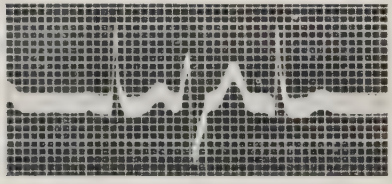
The ventricular extrasystole is followed by an abnormally long pause (T-P interval) preceding the subsequent normal sinus beat. As a rule, the ectopic



A



B



C

Fig. 28. *A*, Premature ventricular beats of multifocal origin. Lead II. Abnormal configuration of QRS. First arises from impulse in left ventricle, fifth from right ventricle. P waves hidden in ventricular complexes.

B, Premature ventricular beats causing bigemini or coupling in a boy, aged 7, with a normal heart. Lead II. Compensatory pause after each premature beat.

C, Interpolated premature ventricular beat. A man, aged 75, with arteriosclerotic heart disease. Lead I. The second ventricular complex is a premature beat interpolated between two normal beats. There is no compensatory pause, the following normal beat coming at its regular time.

ventricular impulse is not conducted retrograde to the atria and the latter are activated at their normal time by the sinus impulse. Since the dominant sinoauricular rhythm is undisturbed, the normal P and QRS which follow the extrasystole also fall at their expected time. The pause after the extrasystole is therefore really compensatory (Fig. 28B). And the P-P interval between the normal beat preceding and the normal beat following the extrasystole is exactly twice the P-P interval between uninterrupted normal beats. Slight variations may be due to sinus arrhythmia.

Rarely, however, the ectopic ventricular impulse is conducted retrograde and activates the atria as well as the ventricles.[73] This occurrence is documented electrocardiographically by inverted P waves in leads II and III following the bizarre QRS of the ventricular extrasystole.

SITE OF ORIGIN OF VENTRICULAR PREMATURE BEATS. The electrocardiogram permits a differentiation between premature beats arising in the left or right ventricles and probably also between those arising at the apex, base or near the septum. These distinctions are based on electrocardiographic records made while ventricular premature beats were induced by electrical stimulation of human hearts exposed during operations for pericarditis.[4, 58, 54]

It is now generally believed that the electrocardiographic configuration of left and right ventricular extrasystoles is exactly opposite to that formerly depicted on the basis of experimental observations in dogs.[51, 72] (See also discussion under bundle branch block, p. 307.) *Right ventricular extrasystoles* are characterized by slurred, notched and widened QRS complexes with the main deflection (i. e., the deflection of greatest duration) upward in lead I and usually downward in lead III. Conversely, *left ventricular extrasystoles* have the main deflection of the bizarre QRS complex downward in lead I and usually upward in lead III.

Basal ventricular extrasystoles are usually characterized by bizarre QRS complexes with main deflection upward in all three leads.

Apical ventricular extrasystoles are usually characterized by bizarre QRS complexes with main deflection downward in all three leads.

Septal ventricular extrasystoles are characterized by QRS complexes which hardly differ from the normal because the ectopic impulse, like supraventricular impulses, reaches both ventricles almost simultaneously. The QRS may be slurred, notched and of very low voltage in lead I.

It should be noted that the localization of various premature beats may not correspond to the above description when the extrasystoles arise near the dividing line between the left and right ventricles and between base and apex. The position of the heart in the chest wall may modify the electrocardiographic conformation of right and left ventricular extrasystoles.[49, 65]

When premature beats in a given electrocardiographic lead are seen to arise from different sites, as indicated by the direction of the QRS complex, they are termed multifocal extrasystoles or bidirectional extrasystoles. They are often indicative of digitalis intoxication or of severe myocardial disease.

Interpolated Premature Beats. The term extrasystole, used synonymously with premature beat, is misleading in that there is actually no extra beat, the precocity of the premature beat being compensated by the subsequent pause before the next normal sinus-controlled ventricular contraction. The premature ventricular contraction merely takes the place of a normal sinus ventricular contraction which fails to appear because the ventricles are refractory. But occasionally, when the heart rate is slow, a premature beat may occur so early in diastole that it is completed in time to permit the next sinus impulse to elicit a ventricular contraction. Here the premature beat is added between two normal beats in their normal rhythm, and is actually an *interpolated extrasystole*[18] (Fig. 28C). The normal beat after the extrasystole may be slightly delayed and its P-R interval prolonged due to a partially refractory state of the conduction system. The normal beat after the interpolated extrasystole is usually a small contraction due to incomplete filling in the brief diastole between the extrasystole and following contraction. The extrasystole itself produces no pulse wave because it occurs so early in diastole that ventricular filling is minimal.

Etiology of Premature Beats. The clinical causes of premature beats are

uncertain as there is no direct evidence of mechanisms identical with those which induce extrasystoles in the experimental animal (p. 248). It is probable that premature beats in man may follow stimuli which reflexly stimulate the vagus and sympathetic nerves, e. g., the premature beats occasionally induced by painful stimuli, carotid sinus pressure, breath holding or forced respiration, and perhaps others of less certain origin.

In clinical practice, the majority of patients with premature beats are not found to have organic heart disease.[56, 10] On the other hand, the presence of heart disease has a distinct tendency to increase the occurrence and frequency of premature beats. Atrial premature beats tend to occur in association with disease or enlargement of the atria, e. g. in cases of mitral stenosis or cor pulmonale. In noncardiac patients, premature beats usually appear without apparent cause, but they sometimes seem to be related to emotional stress and conflict, mental or physical fatigue, irregular sleep and digestive disturbances, especially when these are combined with excessive smoking or drinking of alcohol or coffee. But the relationship is obscure in that only certain individuals are susceptible to premature beats when exposed to the above factors and the same individual does not always respond with premature beats to apparently identical stimuli.

Premature beats have been noted in patients with biliary and renal colic as well as with chronic disease of the biliary tract. A causal relationship is unproven. Infections of various types, especially when associated with fever, have been said to favor the development of premature beats, but without strong evidence. Premature beats have been recorded as being related to cerebral lesions.[48] The occurrence of premature beats is so frequent that a causal relationship to any given factor is usually difficult to prove or exclude.

Age. Premature beats occur at all ages but rarely in infancy and childhood. They have been heard during auscultation of the fetal heart sounds and confirmed by electrocardiograms taken immediately after birth.[3] After the age of fifty the frequency increases notably, and after seventy premature beats occur intermittently in almost all individuals.

Symptoms of Premature Beats. Most persons with premature beats are unaware of their presence. But often there is a momentary, more or less disturbing local discomfort in the precordium. The greatest discomfort has usually been attributed to the long compensatory pause after the premature beat or to the strong contraction that follows. But Kline and Bidder[46] demonstrated that the disagreeable sensation was due to the premature beat or the compensatory pause, and Ungerleider and Gubner[81] indicted the *premature beat* alone as the cause of discomfort.

There may be a sensation of stoppage of the heart, momentary faintness or dizziness and intense associated anxiety. The normal beat after the premature contraction is experienced as a strong thump against the chest wall, as the ventricle expels its unusually large content accumulated during the long diastolic pause. The entire sequence of extrasystole, long pause and strong beat produces an irregularity which evokes a distressing heart consciousness or palpitation which may be described as an oppression, fluttering, thumping, skipped beats, or a sinking feeling. Occasionally the discomfort is localized in, or radiates to the neck, where the patient experiences a fullness, tightness, pulsation or wave reaching to the top of the head. This may be caused by the

regurgitant stream from the right atrium to the neck veins, when the atrium contracts simultaneously with the ventricle and the tricuspid valve is shut.

When runs of extrasystoles occur, general symptoms such as anxiety, pallor, sweating, nausea, weakness, dizziness, faintness and breathlessness may ensue. It is often difficult to determine to what extent these symptoms are of psychic or of circulatory origin. There may be distinct pain simulating that of angina pectoris.

Premature beats often become annoying when the patient is at rest and apparently relaxing, especially when he retires for the night. It is uncertain whether slowing of the heart rate at such times predisposes to their appearance or whether the absence of other distractions makes the patient more aware of their existence. Conversely, exercise often seems to eliminate the premature beats. In fact they are often eliminated at least temporarily by any factor which increases the heart rate, e. g. exercise, atropine, nitrites. In some patients, however, especially in patients with organic heart disease, premature beats are induced by exercise.

Physical Signs and Diagnosis of Premature Beats. *Auscultation of the heart* detects the premature beat which occurs too early in the cardiac cycle and is followed by a longer pause than normal. The premature beat may be similarly recognized at the pulse, but often the premature contraction is too weak to produce a palpable pulse wave.

Both sounds of the premature contraction are usually audible, but only the first sound may be heard if the ventricular contraction is too slight to open the semilunar valves. The extrasystolic heart sounds may be dull and almost inaudible if the ventricle contracts when it is very incompletely filled, or more often there may be a sharp snapping first sound. By a simultaneous phonocardiographic and electrocardiographic study, Cossio et al.[13] found that in 15 of 16 patients with auricular extrasystoles, the first sound of the extrasystole was always louder than the first sound of the preceding or following normal systole. In cases of ventricular premature beats, the first sound was usually louder but occasionally of normal or diminished intensity. When the first sound of the extrasystole was louder, it was also delayed in onset relative to the onset of the QRS. The increased intensity and delayed onset depend on the degree of prematurity and the consequent position of the a-v cusps. With premature contractions the a-v cusps are lower than normal at the onset of ventricular contraction. More time therefore elapses before the valve is closed and this is associated with increased motion, increased vibration and increased intensity of sound. Splitting of the first sound is due to asynchronous contraction of the ventricles which occurs only with ventricular premature beats. This asynchronism accounts also for the lower incidence of intensified first sounds with ventricular extrasystoles.

Diagnosis. Premature beats are usually recognized easily by auscultation and less regularly by palpation of the radial pulse. Sometimes they occur so infrequently that they are absent at the time of physical or electrocardiographic examination, but their occurrence may be suspected from the patient's description.

The electrocardiogram is essential for definite diagnosis and localization of premature beats (p. 250). Ventricular extrasystoles are usually distinguishable from auricular or nodal extrasystoles by the widening, notching and

slurring of the QRS in the former, and the relatively normal QRS complex in the latter two. The P wave in auricular premature beats precedes the QRS; the P-R interval is normal and the T-P pause is longer than normal but not compensatory. The P wave in nodal premature beats is inverted in leads II and III, may follow, be fused with or precede the QRS complex. But if it precedes, then the P-R interval is abbreviated to less than 0.12 second.

Clinical differentiation between auricular, nodal and ventricular premature beats is extremely difficult, but may be successful, based on the following observations. Ventricular extrasystoles are followed by a compensatory pause which permits the next beat to occur at the same time as if there had been no premature beat. On the other hand the pause after an auricular extrasystole is incomplete and the following normal beat occurs too early in the basic rhythm, as may be determined by meticulously and rhythmically counting and tapping with a pencil or with the foot. A striking systolic "a" pulsation in the neck may accompany a nodal or ventricular extrasystole instead of the normal systolic collapse, since the atrium may contract at the same time that the tricuspid is closed by the nodal or ventricular extrasystole. Interpolated extrasystoles may be suggested by the occurrence of three beats in rapid succession in the time normally occupied by two and without a long pause. In trigemini, three beats in rapid succession are followed by a long pause.

When multiple premature beats recur frequently, they may be confused with auricular fibrillation on clinical examination. The rate of the latter is usually rapid (120 or more) unless the patient has been digitalized. Increase of the heart rate by exercise or the administration of nitrites will often eliminate the extrasystoles but not auricular fibrillation. Careful auscultation discloses that the long pauses in extrasystoles are preceded by a premature beat; with auricular fibrillation there are pauses without preceding premature beats. The electrocardiographic distinction is simple.

Extrasystolic bigemini may be distinguished from cardiac alternans (p. 66) by auscultation which reveals even spacing in time in alternans, while there are briefer and longer intervals in bigemini.

Sinus arrhythmia and heart block may produce an irregularity resembling frequent premature beats. Electrocardiographic study is desirable for differentiation. Careful auscultation discloses that the irregularity in sinus arrhythmia is one of increasing and diminishing frequency of beats, often related to the phases of respiration, and may be abolished by exercise (p. 241). In heart block, there is usually a bradycardia and the irregularity is not characterized by premature beats which are always followed by a long pause.

Prognosis. As a rule, premature beats are of no clinical importance. They appear in isolated fashion, at infrequent intervals and produce minimal momentary symptoms or none at all. They are usually unaccompanied by organic heart disease. Observations of patients with premature beats over periods of twenty-four to sixty-seven years have been recorded.[56, 35, 16] When heart disease is present, its diagnosis and prognosis should be based on findings independent of the extrasystoles.[56] The presence of premature beats per se without associated heart disease rarely has significance as to longevity, or as to suitability for life insurance, military service or employability. However, when extrasystoles accompany certain forms of heart disease, the mortality rate may be greater than when the rhythm is entirely normal.[7] Occasionally the frequency of the extrasystoles or the anxiety associated with their occurrence

produces symptoms of a severity out of proportion to their prognostic unimportance.

Auricular premature beats may be clinically more important because of the greater likelihood of underlying heart disease. Their presence should initiate an especially careful search for rheumatic heart disease with mitral stenosis. In patients known to have mitral stenosis, they may represent harbingers of impending auricular tachycardia, flutter or fibrillation. However, even auricular premature beats are not of serious prognostic significance when there is no underlying heart disease.

Ventricular premature beats are often of serious import when they are multifocal, i. e., when they come from several different sites in both ventricles, as seen in a given lead of the electrocardiogram. This finding may denote advanced myocardial disease and impending ventricular tachycardia or fibrillation. But it may also be indicative of *reversible* myocardial irritation due to digitalis intoxication. Extrasystoles forming bigeminal rhythm are commonly due to digitalis intoxication. When they occur with small doses of digitalis, they are said to imply an unfavorable course.

Treatment. Premature beats are usually asymptomatic and require no treatment. When, as is often the case, the extrasystoles are first discovered on routine examination and are unknown to the patient, attention should not be directed to their presence. However, in exceptional circumstances it may be preferable to state their presence and explain their insignificance if it is likely that the patient will see some other physician who may alarm him. If the patient is aware of their occurrence, no treatment is usually necessary except convincing the patient that he has no heart disease. In the absence of heart disease the patient may receive special encouragement if he is told that none of his activities need be restricted. Whether or not heart disease is associated, the patient sometimes needs assurance that nothing dire will eventuate.

Treatment is indicated when the symptoms due to the extrasystoles are distressing despite reassurance. Possible irregularities in hygiene should be corrected even if no definite causal relationship can be proven. The patient should obtain adequate sleep and sufficient periods of both relaxation and simple exercise. Constipation should be corrected. The diet should consist of bland, easily digestible foods and the caloric intake should be diminished if the patient is obese and has been gaining weight. A cholecystectomy or dietary correction of symptoms due to disease of the biliary tract or peptic ulcer may be followed by disappearance of the premature beats. Emotional stresses should be eliminated if possible. Sometimes a vacation with change of environment may be necessary and helpful. Sedatives such as phenobarbital, chloral hydrate or bromides may be beneficial.

Aside from these general measures, it is advisable to eliminate smoking, alcohol and coffee completely at least for a reasonable test period. If the premature beats disappear or become tolerable, resumption in moderation may be tried if desired. When premature beats occur in bigeminal or multifocal form during digitalis therapy, digitalis should be discontinued.

More *specific treatment* consists of the administration of *quinidine sulfate* (p. 279) beginning with an initial test dose of 0.2 gm. (3 grains) and followed by 0.3 to 0.6 gm. (4½ to 9 grains) three to six times daily for a trial period of a week.[85, 60] If desired, these dosages may be attained by progressive increases. If the extrasystoles disappear, a maintenance dose may be deter-

mined by gradual reduction of the dose. Eventually it should be discontinued. In the presence of congestive heart failure, quinidine is usually contraindicated; treatment should be directed to the heart failure and not to the extrasystoles. Sometimes digitalis in doses of 0.1 gm. three times daily for three days, followed by 0.1 gm. daily, is effective whether or not heart failure is present, and even when quinidine has failed. Potassium chloride, phosphate or acetate may also be tried in doses of 2 to 4 gm. (30 to 60 grains) three or four times daily, dissolved into a 25 per cent solution and suitably flavored.[75] Potassium salts may be specially effective in the treatment of extrasystoles due to digitalis intoxication.[74]

Atropine, 0.3 mg. (1/200 grain) three times daily (and increased to tolerance if necessary), has also been effective in treating some patients with premature beats, but I have not observed such favorable results.

In most instances in which treatment appears desirable, the premature beats disappear sooner or later, whether because of, or independently of these drugs. Occasionally they persist stubbornly despite the trial of every available measure.

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12

THE ECTOPIC TACHYCARDIAS

The ectopic tachycardias denote abnormally rapid cardiac rhythms in response to impulses arising outside the sinoauricular node. They are also termed paroxysmal tachycardias because of their frequent occurrence in attacks of cardiac acceleration which start and stop abruptly. They include:

1. (Auricular and nodal) paroxysmal tachycardia.
2. Auricular flutter.
3. Auricular fibrillation.
4. Ventricular tachycardia.
5. Ventricular fibrillation.

Like premature beats, these tachycardias are engendered by stimuli which arise in ectopic centers in the atria or ventricles; they are therefore classified as ectopic rhythms. They are distinguished in this respect from sinus tachycardia in which the rate is also rapid but the controlling impulse arises normally in the sinoauricular node. The ectopic focus responsible for premature beats dominates the rhythm of the heart intermittently, while that responsible for paroxysmal tachycardia becomes the pacemaker for shorter or longer continuous periods.

The paroxysmal tachycardias are considered separately because it is the rapid heart rate more than any other feature of a cardiac arrhythmia which produces serious circulatory disturbances. As a rule the arrhythmias hardly derange circulatory function and provoke little local precordial discomfort, provided the heart rate is slow or normal. Bradycardias, even of intense degree, whether regular or irregular, are also rarely responsible for circulatory distress unless the interval between beats exceeds 3 seconds. Within a reasonable range, a satisfactory circulation is maintained regardless of rate or rhythm, provided there is an adequate interval for myocardial recovery and ventricular (diastolic) filling. On the other hand these essential events become progressively restricted with increasing cardiac rate (p. 9).

Ordinarily paroxysmal tachycardias are transient while the dominant rhythm is of sinus orgin and the rate is normal. Sometimes runs of auricular, nodal or ventricular systoles, termed *repetitive paroxysmal tachycardia*,[95] are almost constantly present for months or years and thus become the dominant rhythm, while normal sinus rhythm interrupts only transiently. Such paroxysms consist chiefly of auricular tachycardia, less commonly of ventricular tachycardia, but also of nodal tachycardia, auricular flutter or fibrillation. Organic heart disease

is usually absent. Palpitation, independent of exertion, dyspnea and syncopal attacks are the commonest symptoms. The prognosis is good and the paroxysms in children disappear during adolescence. Those in adults tend to subside spontaneously. Drug treatment is usually ineffective.

AURICULAR PAROXYSMAL TACHYCARDIA

This is the common form of recurrent palpitation associated with very rapid but extremely regular heart rates.[16, 9] Auricular paroxysmal tachycardia is observed many times as frequently as ventricular tachycardia. A distinction between paroxysmal tachycardias initiated in the a-v node and those initiated elsewhere in the atria is extremely difficult or impossible.

Mechanism. It has been assumed that auricular paroxysmal tachycardia, like auricular extrasystoles, results from a rapid succession of rhythmic impulses arising in an irritable ectopic focus in the atrium.[71] The possibility also that this ectopic focus is a parasystolic center protected by local blocks has been suggested by advocates of the theory of parasystole (p. 249). More recently the theory of circus rhythms, generally invoked to explain auricular flutter and fibrillation (p. 272), has been expanded to apply also to auricular paroxysmal tachycardia. The evidence for this belief has been summarized by Barker, Wilson and Johnston,[6] who suggested that auricular paroxysmal tachycardia is due to a special kind of circus rhythm (reentry) which involves the sinoauricular or the auriculoventricular node in its pathway. The abrupt onset and termination of attacks, the remarkable constancy of rate, the slowing of the auricular rate and abolition of the attack by quinidine, the occasional alternation of cycle length, the occasional occurrence of auriculoventricular block and the occasional association of paroxysmal tachycardia with auricular flutter and fibrillation[29] are all features suggesting an underlying circus rhythm and a close relationship between auricular tachycardia, flutter and fibrillation. But curves of the momentary atrial electrical axes suggest that the auricular tachycardia unlike flutter and fibrillation is not due to circus movements.[29] An essential distinction is the separation of the auricular deflections by isoelectric intervals in auricular tachycardia, whereas in auricular flutter the electrocardiographic oscillations are continuous and there is no isoelectric interval between P waves.

The auricular rate varies usually between 150 and 220 per minute, but most commonly between 180 and 200. The ventricles almost always respond to each auricular beat. But recently series of cases have been collected in which there was an associated auriculoventricular block, usually 2:1.[28] In infants, auricular paroxysmal tachycardias occur in which the auricular rate is as high as 300 per minute and yet there is a 1:1 ventricular response.[62, 123] However the differentiation of these cases from auricular flutter is uncertain. The auricular rate of 160 to 240 in auricular paroxysmal tachycardia compares with an auricular rate of 250 to 320 in auricular flutter and 350 to 500 in auricular fibrillation. The progressively greater frequency of a-v block in the latter two conditions is explainable by the more frequent auricular impulses attempting to traverse the a-v node and bundle.

The Electrocardiogram. The characteristic feature is a rapid, regular series of ventricular complexes (RT waves) with the T wave slightly modified by fusion with the P wave (Fig. 29). The QRS complex is usually of relatively normal contour but in prolonged paroxysms, especially with ventricular rates

exceeding 200 per minute, the QRS may become widened, notched and slurred due to impaired intraventricular conduction.

The P waves, though present, are difficult to identify because the abbreviated interval between beats causes them to fuse with the preceding T. When identified, the P waves may be upright and relatively normal in contour, suggesting that the auricular impulse originated near the sinoauricular node, or the P waves may be inverted in leads II and III suggesting an origin in or near the a-v node. The P waves in auricular tachycardia may be best identified by taking esophageal leads[17] or a precordial lead from the right side of the sternum.[35] In this manner also the occasional occurrence of a-v block (usually 2:1) in auricular paroxysmal tachycardia may be discovered.[21, 35]

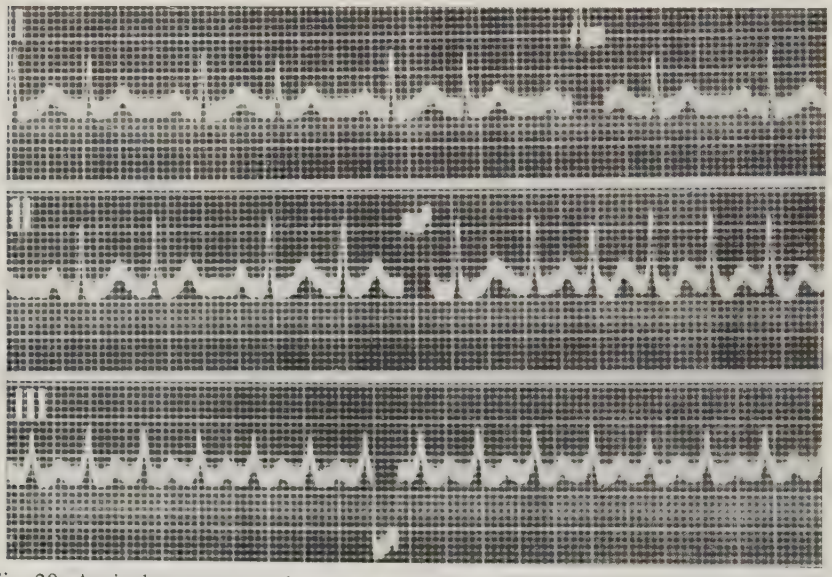


Fig. 29. Auricular paroxysmal tachycardia. Occasional premature auricular premature beats in leads I and II preceding onset of auricular tachycardia in lead II and continuing in III. Ventricular configuration resembles normal complexes in lead I. P and T fused. Rate 190 per minute.

The onset of a paroxysm, as observed in electrocardiograms, commences abruptly with a preliminary extrasystole; its termination is likewise abrupt, a brief pause intervening before the prompt resumption of sinus rhythm.

Etiology. The etiology of auricular paroxysmal tachycardia is obscure. The same nervous, toxic and digestive disturbances, emotional stress, fatigue, exertion and disease of the biliary tract, which have been held responsible for premature beats, have also been indicted as responsible for attacks of auricular tachycardia. Chronic auricular tachycardia, with slowing of the heart rate and occasional sinus rhythm with recumbency only, has been reported.[88]

Heart disease is usually absent, but evidence of rheumatic cardiovalvular disease is not uncommon.

Paroxysmal auricular tachycardia occurs at any age; possibly it is most common between twenty and forty. It has been reported in infancy.

Symptoms.[132] The onset is sudden and without warning. Often a rapid

change in position of the head or trunk, an unexpected emotional upset or an unpleasant dream appears to unleash the attack. But usually there is no apparent precipitating cause.

There may be a sudden thump or two against the chest wall, a seeming momentary stoppage of the heart or some other precordial discomfort followed by a continuous palpitation, fluttering, racing or pumping of the heart beat. Sometimes there is definite precordial pain, a smothering sensation in the chest and throat, fullness or a sense of pulsation in the neck and head, or epigastric distress. However there may be only mild palpitation or no symptoms at all, especially with relatively slow ventricular rates or with paroxysms of brief duration.

These *local symptoms* are often overshadowed by *psychic and reflex nervous* manifestations, especially when the attacks persist for more than a few minutes. Anxiety or even angor animi, weakness or exhaustion, coldness or sweating, and a sense of smothering may occur early. There may be dizziness, faintness or momentary syncope at the onset. Abdominal distention, gaseous eructations, salivation, nausea or vomiting may occur. Occasionally the vomiting appears to terminate the attack, whether the emesis occurs spontaneously or is induced. There may be polyuria at the termination of the paroxysm.

Serious circulatory disturbances may develop if the rate is exceedingly rapid, but especially if there is underlying cardiac disease and if the paroxysm is prolonged. Although physiologic experiments indicate that acceleration of the heart beyond 180 per minute progressively reduces the cardiac output (p. 9), it is remarkable how often heart rates over 200 per minute are tolerated for many hours or even days without evidence of circulatory insufficiency, provided the heart is otherwise normal. But in hearts with serious organic disease, prolonged tachycardia is very likely to induce failure.

Weakness, pallor, perspiration and coldness of the extremities may be due to a diminished cardiac output. Cerebral ischemia may be responsible for faintness or syncope. In extreme degree, peripheral slowing of the circulation is followed by thrombosis and gangrene of an extremity.

Symptoms and signs of congestive heart failure may also develop. These include dyspnea and cough due to left ventricular failure. Occasionally there is a frothy bloodstained sputum indicative of pulmonary edema. The patient's veins may become engorged and his pallor suffused with cyanosis. The liver may enlarge and the abdomen become painful and tender. The attack may occasionally terminate fatally, either with signs of progressive failure or suddenly. As a rule, however, the paroxysm ends abruptly, normal rhythm is restored and the symptoms and signs of circulatory insufficiency abate rapidly.

The occurrence of pain has been mentioned. Occasionally the pain closely resembles the compressing substernal pain of angina pectoris or cardiac infarction. It may actually be due to functional coronary insufficiency and myocardial anoxia secondary to the tachycardia.

Signs. *Physical examination* usually reveals only the regular rapid heart rate. The rate remains mathematically constant despite changes of position, emotion or exercise.[37] The heart sounds may present a tic-tac rhythm (embryocardia). The heart is usually normal in all other respects. However, cardiac enlargement and murmurs may disclose underlying heart disease. Sometimes enlargement develops only with the occurrence of heart failure; this is re-

versible with restoration of normal rhythm. Murmurs previously present, such as that of mitral stenosis, may disappear during the tachycardia. Therefore, examination at that time may not reveal the underlying disease.

In severe and prolonged attacks the patient may appear obviously anxious or agitated and there may be objective signs of congestive failure.

The pulse is very rapid and small, but regular. However, since the pulse may be very deceptive as to regularity or irregularity, this quality should always be determined by cardiac auscultation.

There may be a prominent and even palpable pulsation of the cervical veins.

The blood pressure often falls during severe or long paroxysms. Under these circumstances the systolic pressure drops more than the diastolic, with a resulting fall in pulse pressure.

Diagnosis. See p. 288 for diagnosis and differential diagnosis of the tachycardias.

Prognosis and Course. Paroxysms of auricular tachycardia stop as abruptly as they begin, either spontaneously or because the patient adopts certain positions, takes a deep breath, holds his breath with glottis closed, or because the physician controls the attack. As a rule, the attacks subside spontaneously in seconds or minutes, but attacks with disturbing symptoms last for several hours and occasionally for several days. They are distinguished from attacks of auricular flutter, which may persist for many days, weeks or even months (chronic auricular tachycardia).[58] However, the attacks of paroxysmal tachycardia which are associated with auriculoventricular block often last for many hours or days and occasionally for weeks or months.

In most cases, paroxysmal auricular tachycardia is of no clinical importance, either from the viewpoint of producing disturbing symptoms or of denoting the presence of organic heart disease. Usually the paroxysms occur rarely at long intervals or a few times in an entire lifetime. Occasionally, however, they recur with some frequency, varying from several times a year to several times a week. Except in rare instances in which they recur frequently or are very prolonged, they neither interfere with gainful work, lead to heart failure, nor shorten life. In some persons, attacks of auricular tachycardia foreshadow the development of auricular flutter or fibrillation. In cases in which there is associated anatomic heart disease, prolonged and severe attacks may lead to congestive heart failure,[50] and rarely to peripheral thromboses and gangrene, Adams-Stokes syndrome, and cardiac infarction with acute coronary occlusion. Heart failure may be induced occasionally also in the apparently normal heart.

Treatment of Auricular Tachycardia. Treatment is directed at (1) control of the acute attack of auricular tachycardia, and (2) prevention of future attacks or diminution of their frequency in persons subject to frequent paroxysms.

The Acute Attack. The acute attack may sometimes be terminated by the patient if he is instructed to try to sit, leaning forward with his head down, to lie prone across the bed with his head lower than his trunk, to take a deep breath with glottis closed after a complete expiration (Müller procedure), or to expire forcibly with glottis closed after a deep inspiration (Valsalva experiment). Sometimes a patient or a member of his family learns to abort the attack by firm (painful) pressure on one eyeball with the eyelid closed (oculocardiac reflex). Induced gagging and vomiting by irritating the pharynx with the finger is occasionally effective. Most of the effective therapeutic measures

restore sinus rhythm by vagal stimulation,[24] which diminishes the rate of impulse production in the sinoauricular and auriculoventricular nodes.

The physician's most useful procedure is to make pressure over the right carotid sinus and, if this is ineffective, over the left carotid sinus for 10 to 30 seconds. The carotid sinus may be located by feeling the strong carotid arterial pulsations at the bifurcation of the common carotid at the level of the upper border of the thyroid cartilage. The patient may be reclining or sitting with his head slightly forward and his neck relaxed. Pressure is best made with two or three fingers, compressing the artery and sinus posteriorly and medially against the vertebral spine. Occasionally a massaging motion is effective. I prefer to listen with my stethoscope or ear against the patient's precordium as I perform the compression. In this way unnecessary prolongation of the procedure is avoided, with the possible risk of syncope or cardiac standstill. Cardiac auscultation is also important because carotid sinus pressure is

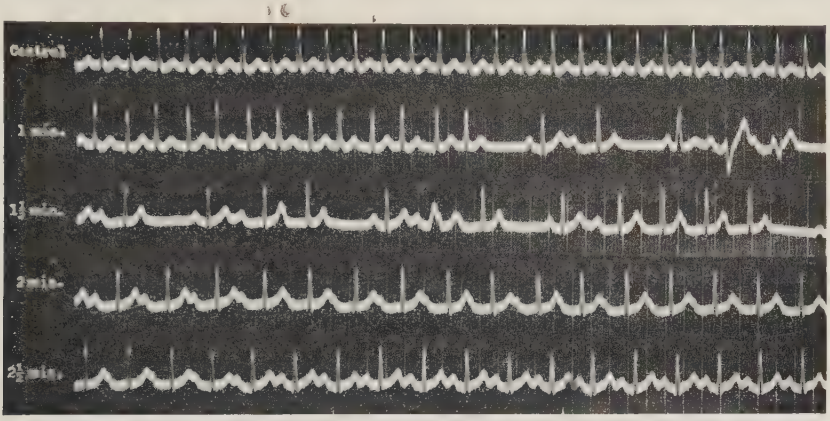


Fig. 30. Paroxysmal auricular tachycardia. Effect of 25 mg. of mecholyl. Occasional slowing with sinus beats after one minute. In lowest strip sinus rhythm with sinus tachycardia, rate 130 per minute. In next half minute normal rhythm with rate of 90.

often useful not only for terminating the attack, but also for the differential diagnosis of the various forms of tachycardia (p. 288). Attention is directed to the occasional occurrence of transient or permanent monoplegia[134] or hemiplegia following carotid sinus stimulation.[11]

A similar vagal reflex may be induced by firm pressure over one eyeball at a time and then if necessary over both eyeballs simultaneously.

If these mechanical measures fail, a number of drugs may be employed, chiefly for their stimulating effect on the vagus nerve.

Mecholyl (acetyl-beta-methylcholine chloride), 20 mg. (1/3 grain), may be administered hypodermically[110] (Fig. 30). If the first injection is ineffective, the same dose is repeated in half an hour. The patient should be in the horizontal position to avoid possible syncope. Mecholyl is contraindicated in allergic patients, especially those with a history of bronchial asthma, because of the drug's tendency to cause bronchial spasm and increased bronchial secretion. Mecholyl is also said to be contraindicated in patients with hyperthyroidism, in whom it is reported to have precipitated auricular fibrillation.[90] Unpleasant and sometimes alarming reactions occur, including extreme flushing of the face, perspiration, intense salivation, a sense of choking or of imminent

death and, rarely, collapse. Nausea and vomiting are not uncommon, but usually at or after termination of the attack. In order to avoid, minimize or abbreviate these reactions, a hypodermic needle and syringe containing 0.6 mg. (1/100 grain) of atropine sulfate should be prepared and available when the mecholyl is administered. If reactions occur, a tourniquet should be applied for several minutes to constrict the venous return above the site of injection and the atropine injected into the other arm. In my experience with auricular paroxysmal tachycardia, mecholyl has almost always succeeded in restoring sinus rhythm within a few minutes. If mecholyl alone and carotid sinus pressure alone are unsuccessful, the combination of both measures may be employed simultaneously and may succeed in restoring normal rhythm. These measures are usually unsuccessful in cases of auricular tachycardia associated with a-v block. Neostigmine, in doses of 1 mg., has also been employed in the treatment of supraventricular tachycardia.[117]

Other recommended measures with which I have had few experiences or little or no success include the oral administration of syrup of ipecac, 8 to 16 cc. (2 to 4 drams), repeated if necessary until vagal stimulation is sufficient to induce vomiting,[120] or the hypodermic administration of apomorphine (5 to 10 mg. or 1/12 to 1/6 grain). Both of these procedures are drastic and rarely necessary. Magnesium sulfate has been recommended, 15 to 25 cc. of a 20 per cent solution being injected intravenously 5 cc. at a time.[138, 10, 135] Similar success has been claimed for the intravenous injection of calcium chloride or gluconate (10 to 20 cc. of a 10 per cent solution),[133] and for the subcutaneous administration of prostigmine in doses of 0.5 to 2 mg.[22] An intravenous injection of 0.4 gm. of atabrine has restored sinus rhythm in a case of nodal tachycardia within 45 seconds.[49] Procaine compounds may be tried.

Digitalis and quinidine are the final dependables in cases which do not respond to the above attempts at rapid restoration of sinus rhythm. Digitalis is the drug of choice in patients with serious underlying cardiac disease, those in whom the attack has caused heart failure, or those to whom quinidine has been administered without success. In urgent cases digitalis or ouabain (strophanthin) may be administered intravenously. Weisberger and Feil[127] administered lanatoside C intravenously, in a dose of 0.8 mg. repeated in thirty to sixty minutes if necessary. In 16 of 17 instances of paroxysmal tachycardia, the tachycardia stopped suddenly within 40 minutes after the first dose; in the remaining case it stopped within 12 hours.

Digitalization may also be effected rapidly with the oral preparation of digitoxin. In general, full doses of digitalis should be given before discontinuing it as ineffective. (For preparations and methods of administration of digitalis, see p. 183.)

Quinidine is sometimes effective when all other measures have failed.[108, 63] Its success in restoring sinus rhythm probably depends on its direct and indirect increase of the refractory period and depression of conductivity of the auricular musculature. (For dosage, administration and toxicity, see p. 279.)

For prolonged attacks which do not respond to other measures, sedatives are usually necessary. Bromides, phenobarbital or chloral are most generally employed. Occasionally morphine is justifiable and effective, especially in the presence of distressing dyspnea, shock or pain, but it is rarely needed and is contraindicated when attacks recur at relatively brief intervals. The applica-

tion of an ice bag to the precordium often affords psychologic and perhaps more specific benefit. Reassurance is important.

Prevention of Attacks. The prevention of frequent attacks of paroxysmal tachycardia is difficult because of ignorance as to the underlying or precipitating cause. All of the measures advised in the treatment of frequent extrasystoles should be employed (p. 257), including the avoidance of emotional tension, fatigue, tobacco, coffee and alcohol, indigestion and constipation.

Among drugs, mild sedatives may be useful, but *quinidine* and *digitalis* are most dependable. The dosage of quinidine may start at 0.3 gm. (5 grains) every two hours for six doses and may be increased gradually up to 4 gm. (60 grains) daily in divided doses if necessary. When the controlling dose is found, it may have to be continued for months or years if the attacks recur when the drug is omitted. Quinidine, thus administered, may eliminate recurrences entirely or diminish their frequency. If an attack occurs despite quinidine administration, mecholyl and other forms of vagal stimulation may be less effective than ordinarily because the quinidine is antagonistic in its action. Digitalis in doses of 0.1 gm. (1½ grains) of the leaf three times daily, or digitoxin 0.1 mg. three times daily for four to six days followed by 0.05 gm. (¾ grain) daily of the leaf or 0.1 mg. of digitoxin daily may be effective when quinidine is not.

AURICULAR FLUTTER

This is a form of rapid heart action in which the atria beat regularly at a rate of 250 to 350 per minute. The term flutter was first employed by MacWilliam[79] to describe the response of the atria to faradic stimulation, but it is uncertain whether he actually observed flutter or fibrillation. Clinical auricular flutter was first described in detail by Jolly and Ritchie in 1910.[64] Usually there is a 2:1 or some other fixed a-v block, and the ventricles beat regularly at rates of 125 to 160 per minute. Ventricular rates as high as 300 per minute may occur, usually in infants, in whom all the auricular impulses produce ventricular contractions. An irregularity of the ventricular rate may result from changing a-v conduction and altered degrees of a-v block.

Auricular flutter is encountered much less commonly than either auricular fibrillation or auricular tachycardia, to both of which it is related in mechanism. Conversion from auricular flutter to fibrillation occurs commonly, especially after the administration of digitalis. Within the same electrocardiogram one may observe portions in which it is difficult to distinguish between auricular flutter and fibrillation or occasional shifts from auricular flutter to fibrillation and vice versa. This is termed impure flutter.

Auricular flutter usually occurs in paroxysms which persist much longer than those of auricular tachycardia, lasting many days, weeks or months. When flutter lasts more than two to three weeks, it is termed established flutter. This type may persist indefinitely unless controlled by therapeutic measures.

Mechanism. Like auricular fibrillation and possibly like auricular tachycardia, auricular flutter is believed to be due to an ectopic impulse which travels in a never-ending circular path—so-called circus rhythm (p. 272). According to Lewis et al.,[75] the impulse in auricular flutter courses around the orifices of the superior and inferior venae cavae. On returning to the ectopic center the impulse finds its site of origin no longer refractory. The original impulse thus reenters the circuit and continues around the same ring of

muscle, usually about 250 to 350 times a minute. According to this theory, the auricular rate is determined by the speed with which the impulse traverses the circuit and this, in turn, by the conductivity, refractory period and length of the circus ring of muscle. In addition to the impulse traversing the single mother circuit, centrifugal excitation waves (depolarizing impulses) spread to the various outlying portions of the atria and result in relatively ineffective but distinctive regular systolic contractions and diastolic relaxations of these chambers. It should be noted that Rothberger[99] and his school adhere to the belief that auricular fibrillation and flutter, like auricular paroxysmal tachycardia, result from rapid stimuli arising in parasystolic foci. The auricular rate in flutter is greater than that in tachycardia and less than that in fibrillation. By taking slow motion pictures (2000 frames per second) of dogs' atria which were made to flutter by aconitine, Prinzmetal et al.[97a] were able to confirm the conclusions of Scherf and associates[104] that atrial flutter is due to rapid stimulus formation in a single focus.

Conduction of all the very rapid auricular impulses to the ventricle is rarely possible. Occasionally in infants and rarely in adults there is a 1:1 ventricular auricular rate, the ventricles contracting regularly 250 to 300 times a minute. But as a rule there are varying degrees of partial heart block (2:1, 3:2, 3:1,

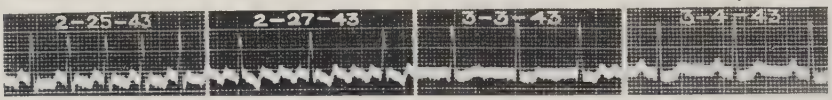


Fig. 31. Atrial flutter. Effect of digitalis. Feb. 25, atrial flutter with 2:1 response. Atrial rate 340. Ventricular rate 170. Feb. 27, 4:1 response. Ventricular rate 85. Patient digitalized. Four days later atrial fibrillation. Digitalis discontinued. Mar. 4, return of regular sinus rhythm.

etc.). Most commonly the ventricular rates vary between 100 and 150 per minute and there is a 2:1 block. With higher degrees of block, e. g., 4:1, the ventricles may beat not only regularly but at normal rates, e. g., 70 to 80. Complete heart block with auricular flutter has also been noted.[64, 51]

The Electrocardiogram. The *P waves* are absolutely regular in rhythm at rates of 250 to 350 per minute (Fig. 31). There is often a sharp upstroke with a more gradual downstroke forming a characteristic series of continuous oscillations without distinct isoelectric intervals. They may present a distinct resemblance to saw teeth. The P waves are best seen in leads II and III of the standard leads, and are indistinct in lead I because the presumed pathway of the ectopic impulse is perpendicular to the direction of lead I whereas its course is more nearly parallel to the direction of leads II and III. Most of the precordial leads do not usually disclose the P waves distinctly; however, the P waves are usually well displayed in leads from the right side of the sternum (CF_1, CR_1). The latter or esophageal leads should always be obtained in the study of any paroxysmal tachycardia, especially in cases in which a rapid ventricular rate obscures the P waves.

The *P-R interval* is prolonged, but it is often difficult to measure. It may vary from beat to beat especially in cases with varying grades of a-v block.[43] Even with unaltered grades of heart block, e. g., 2:1, slight alterations in the R-R interval may result from corresponding changes in the P-R interval.

The *QRS complexes* usually recur regularly at rates of 75 to 150 per min-

ute, except as noted above with changing P-R intervals or degree of a-v block. Rarely there is a 1:1 block with ventricular rates of 250 to 300 or more in infants. In cases of atrial flutter with 1:1 response or even with 2:1 response the P waves may be obscured and the sequence of QRS complexes resembles a ventricular tachycardia (Fig. 32). Atrial flutter with bundle branch block

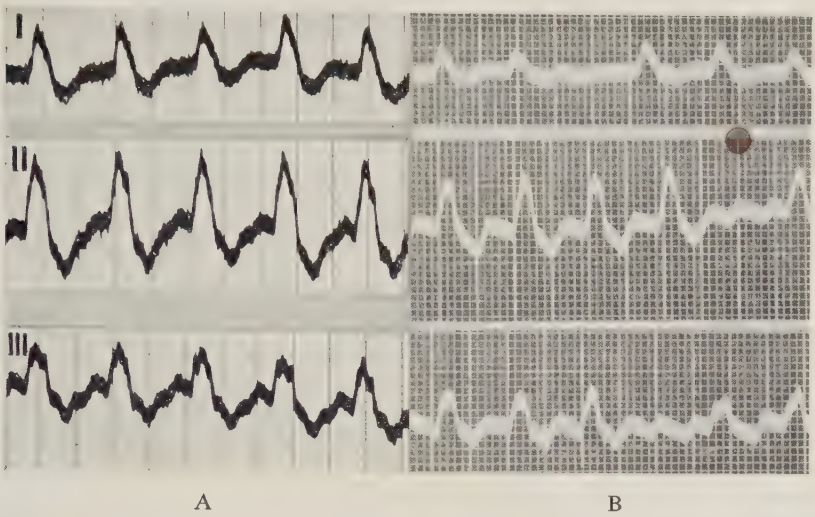


Fig. 32. *A*, Atrial flutter with 2:1 response resembling ventricular tachycardia. Presence of flutter confirmed by jugular venous tracing.
B, Same case. After digitalization flutter waves clearly seen especially in lead III.

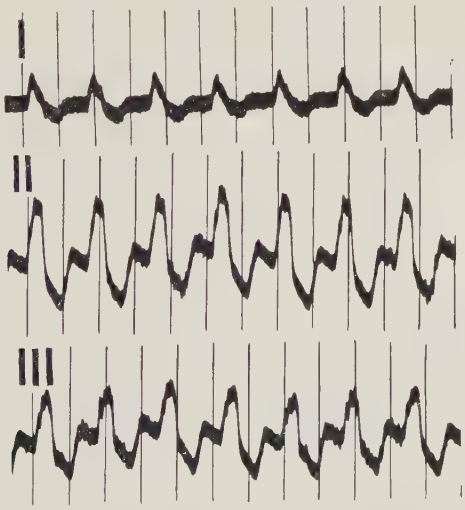


Fig. 33. Atrial flutter with bundle branch block simulating ventricular tachycardia.

may also simulate ventricular tachycardia (Fig. 33). Most commonly a QRS complex follows every second P wave, occasionally every third or fourth P wave. In such instances every second, third or fourth P wave may be fused with or obscured by the QRS complex. In long electrocardiographic strips there may be seen changing grades of block, but usually there is a dominant

degree of heart block. Similarly, the P-R interval may vary in length, but there is a tendency to return to a dominant time interval.[43]

If an electrocardiogram is taken during carotid sinus pressure, the auricles are found to be unaffected, while the ventricular rate is slowed and the degree of a-v block may be increased. Occasionally, momentary cardiac standstill may occur. These effects result from vagal stimulation which impairs conduction through the a-v node. Digitalis usually produces similar effects.

Etiology. Auricular flutter, like fibrillation and unlike auricular tachycardia, is observed more commonly with heart disease than in its absence. Its greatest frequency is with rheumatic heart disease and mitral stenosis, but it may also be associated with hyperthyroidism (p. 920) or with coronary arteriosclerotic and hypertensive heart disease.[93] The tachycardias of infancy, occurring usually in the first month of life, are generally unaccompanied by an underlying cardiac affection, but may be due occasionally to rhabdomyoma of the conduction system or other myocardial disease. Auricular flutter may be observed with mediastinal disease, and during surgical procedures, especially those in the thoracic cavity. Not infrequently it appears in patients without apparent heart disease, either spontaneously or because of alleged nervous or physical strain or respiratory infection.

Symptoms and Signs. The symptoms are those of any sudden paroxysmal tachycardia, namely palpitation, anxiety ranging to alarm of impending death, weakness, dizziness or syncope, and possible symptoms and signs of congestive heart failure or shock, as detailed under paroxysmal auricular tachycardia (p. 263).

Most if not all of the paroxysmal tachycardias of early infancy with auricular and ventricular rates of 250 to 300 are probably examples of auricular flutter. While the tachycardia may be discovered accidentally, it is usually documented by the infant's refusal to take food, vomiting, restlessness, pallor, and later cyanosis, striking rapid enlargement of the liver, dyspnea with noisy respiration, pulmonary edema and other evidences of congestive heart failure.[62, 7, 123]

The heart rate in auricular flutter is rapid and usually regular despite rest, exercise or change of posture. Auscultation of the heart discloses apical rates of 125 to 160 when there is 2:1 block, but the rate may be 75 or 100 with blocks of 4:1 or 3:1 respectively. Sometimes there is a sudden change in rate from 160 to 80 as the degree of block alters from 2:1 to 4:1. When the ventricular response and therefore the cardiac beat are irregular, exercise may raise the ventricular rate and induce a constant degree of block and a regular heart beat. A changing intensity in the first heart sound in cases with irregular ventricular response may be due to the alterations in the P-R interval.[54]

Inspection of the cervical veins may disclose distinct "a" waves of auricular contraction which are two, three, four or more times as frequent as the apical (ventricular) waves. When present, these "flutter" waves are diagnostic.

There may also be physical signs of an underlying cardiac disease or of associated circulatory failure.

Prognosis. The attack of flutter is apt to be more disturbing than that of auricular tachycardia because of its greater tendency to persist (days, weeks, months or years).[39] Cases of auricular flutter lasting eleven years[66] and twenty-four years[74] have been reported. Because of the prolonged duration and the frequency of underlying heart disease, auricular flutter is apt to be complicated by the development of congestive heart failure. However, it is remarkable how

patients with normal hearts, despite auricular flutter, or with ventricular tachycardia of months' or years' duration suffer no visible deterioration of their cardiac function. Sometimes the attacks are disabling by their very persistence even when circulatory function remains adequate. Embolization occurs occasionally. Relapses of flutter occur frequently after sinus rhythm has been restored. Often auricular flutter is followed sooner or later by auricular fibrillation. This may occur spontaneously or in response to digitalis therapy.

Treatment. Treatment consists essentially in the administration of digitalis or quinidine. Digitalis is usually given first trial and should certainly be chosen if there is evidence of congestive heart failure. The digitalis should be given in full doses, i. e., until the desired therapeutic effect is obtained. Often distinct signs of toxicity appear with effective dosage. (For doses and methods of digitalization, see p. 183). The ventricular rate is usually reduced to the normal range by an increase in the degree of a-v block, or the flutter is converted to auricular fibrillation and the ventricular rate is gradually slowed to desired levels. In either circumstance, daily doses of digitalis leaf, 0.05 to 0.1 gm. (¾ to 1½ grains), or digitoxin, 0.1 mg. to 0.2 mg., are continued as required to maintain the desired apical rate. Often, in cases with induced auricular fibrillation, discontinuation of the digitalis is followed by a reversion from auricular fibrillation to normal sinus rhythm. If not, the necessary doses of digitalis should be resumed or an effort be made to restore normal sinus rhythm with quinidine.

Quinidine may be administered as described below under auricular fibrillation (p. 279), either (1) at the outset, in cases without apparent cardiac disease or heart failure, (2) in cases in which digitalis has been found ineffective, or (3) in those cases in which omission of the digitalis after induced auricular fibrillation is not followed by a resumption of sinus rhythm. In cases of frequent, relapsing auricular flutter, quinidine may also be given after an attack is controlled, in the hope of preventing or minimizing recurrences.

Reassurance, avoidance of emotional and physical stresses when possible and elimination of tobacco, coffee and alcohol, indigestion, constipation and other factors which may seem to contribute to the attacks should all be considered as accessory therapeutic measures.

AURICULAR FIBRILLATION

This is an arrhythmia characterized by extremely rapid irregular auricular impulses, by ineffectual vermicular auricular contractions, and by irregular rapid ventricular beats. Cushny and Edmunds[26] first interpreted auricular fibrillation in man as synonymous with the perpetually irregular pulse of Hering[56] and the physiologist's delirium cordis. Rothberger and Winterberg[100] and independently Lewis[72] proved this electrocardiographically.

Auricular fibrillation is one of the two or three commonest and probably the most important of all the disorders of the heart beat. It may occur as paroxysms of an irregular tachycardia or more often it becomes established as a permanent condition.

Mechanism. Auricular fibrillation, like auricular flutter, is most generally regarded as resulting from an ectopic stimulus which repeatedly courses along a ring of atrial musculature (circus rhythm). However, this theory has been challenged by Rothberger[99] and others,[104, 97a] who assume that auricular flutter and fibrillation are initiated by rapid impulse formation in a single center.

Auricular fibrillation differs from flutter in that the stimulus recurs or retraces its path at much more rapid rates (400 to 600 per minute as compared with 250 to 320) and the impulse traverses its circuit irregularly instead of regularly as in flutter.

Circus Rhythms. Circus rhythms or circus movements were first induced in the umbrella of the jelly fish by Mayer,[82] who blocked a local area and applied a stimulus on one side of the block. The excitation wave thus initiated traversed the ring of the umbrella in a unidirectional fashion away from the block. If on completing the circuit and reaching the previous site of the block near its origin, the impulse (or wave) found the block gone and the tissue therefore no longer refractory, it continued to circle the ring a second, third, fourth time, etc. If no block had been set up at the original moment of stimulation, an excitation wave was able to spread along the ring in both directions (clockwise and counterclockwise) from its origin until both forward portions met and neutralized each other halfway along the circumference.

Further researches by Mines,[89] by Garrey[46] and by Lewis and his associates[75] disclosed that circus rhythms depended on (1) extreme shortening of the refractory period of the heart muscle, (2) slowing of the rate of conduction of an excitation wave, (3) local areas of block (or depressed excitability) and (4) rings of sufficiently large circumference. The causative mechanism in human auricular fibrillation is uncertain, but it is probable that local blocks which are essential for circus movements may be set up by disease of the auricular muscle and by auricular dilatation. In patients without organic heart disease, the autonomic nerves, especially the vagus, may be the direct or indirect initiating agents.[90, 2]

Support for the theory of circus movement was recently found in curves of the momentary atrial electrical axes.[30] In cases of atrial flutter and fibrillation, the curves of these axes were roughly circular, while the curve in cases of paroxysmal tachycardia resembled that of sinus rhythm.

Auricular Behavior. In pure auricular flutter, the impulse is believed to traverse its circus path at an absolutely regular rate. From this excitation wave, sometimes called the central or mother wave, centrifugal waves are believed to flow uniformly and regularly to the various parts of the auricular musculature. This results in weak but distinct auricular contractions. In auricular fibrillation, the basic ring is shorter and the frequency of circulation of the excitation wave is much greater. For these reasons the wave is believed to traverse the ring irregularly, i. e., it must keep deviating in its pathway to avoid areas of block. Similarly the centrifugal waves also are deflected irregularly in their course and vary from cycle to cycle. In consequence, no definite coordinated universal auricular systolic contraction or diastolic relaxation can occur. Instead auricular fibrillation is characterized by continuous dissociated contractions of some, and relaxation of other groups of fibers, which produce worm-like (fibrillary) quiverings of the atria without an effective auricular contraction. So-called impure flutter or flutter-fibrillation represents an intermediary or transition phase between flutter and firbillation, combining features of both disturbances.

Ventricular Behavior. Like auricular flutter, auricular fibrillation is associated with various degrees of a-v block. But because of the more rapid auricular rates in fibrillation, fewer impulses can reach or excite the ventricles and because the auricular rhythm is irregular the ventricular rhythm in auricular

fibrillation is also irregular. Only about one out of three or one out of four auricular impulses gains access to the ventricles, and consequently the ventricular rate usually varies between 100 and 140 per minute. In patients without organic heart disease and in the paroxysmal type of auricular fibrillation, higher rates even approaching 180 to 200 may be observed.

Under certain circumstances auricular fibrillation is associated with ventricular contractions which are *irregular in rhythm* but *normal or slow in rate:*

1. In *partial heart block* due to underlying rheumatic myocarditis, calcific aortic stenosis or severe coronary artery disease, the ventricular rate may range between 90 and 40 per minute.

2. *Carotid sinus pressure,* by causing reflex vagal stimulation, depresses a-v conduction and slows the ventricular rate.

3. *Digitalis,* by direct action on the a-v node and bundle, diminishes auriculoventricular conduction and in therapeutic doses may slow the ventricular rate to between 60 and 80 per minute. Thus when patients with auricular fibrillation are adequately digitalized, their heart beat, if sufficiently slowed, may appear to be regular. The irregularity becomes clear if the rate is increased by exercise or amyl nitrite.

Under other circumstances the *ventricular contractions* in cases of auricular fibrillation may actually become *regular* with slow or rapid rates as follows:

1. *Complete heart block* in association with auricular fibrillation. No auricular impulses are transmitted to the ventricles and the latter respond regularly and slowly to their own pacemaker (idioventricular rhythm). Exercise does not restore the irregularity.

2. *Ventricular paroxysmal tachycardia.* The ventricles respond rapidly and regularly to stimuli from an ectopic ventricular center and prevent excitation by stimuli from the fibrillating atria.

3. *Digitalis intoxication* may block the auricular impulses and cause a-v dissociation (resembling but not identical with complete heart block, see p. 246). The ventricle beats regularly at rates of 40 to 80 per minute in response to a ventricular pacemaker.

Effect on Cardiac Function. The absence of effective auricular contraction removes a significant factor in the filling of the ventricles. According to the observations of Lewis[73] and of Wiggers and Katz[126] this may amount to 20 to 30 per cent of the total ventricular contents. Studies of cardiac output suggest that it is considerably reduced during auricular fibrillation, for with the restoration of sinus rhythm the cardiac output increases 25 to 30 per cent.[65, 113] According to Harrison and his associates[53] the cardiac output is only slightly diminished in cases of auricular fibrillation, but in the presence of congestive heart failure the cardiac output is essentially the same whether the atria are fibrillating or normal sinus rhythm holds sway. These rather divergent findings may depend on difficulties in the technic as well as differences in the types of cases. From the clinical viewpoint, it appears that fibrillation of the atria does not significantly impair cardiac function if the ventricular rate is sufficiently slowed to permit adequate diastolic filling.

The Electrocardiogram. The characteristic electrocardiographic features of auricular fibrillation are (Fig. 34):

1. *Absence of P waves.* But there are usually continuous, slight undulations known as "f" or fibrillation waves. Sometimes these are visible only in precordial leads taken from the right side of the sternum or in esophageal leads.[91,19]

2. *Irregularly spaced QRS complexes.* They also vary somewhat in their configuration. Occasionally notching, slurring or widening of the QRS complex (intraventricular conduction disturbance) due to fatigue of the conduction tissues is observed in cases with ventricular rates of 180 or more.

In cases of impure flutter there are occasional series of regular or almost regular P waves which vary in contour. However, the R-R intervals change from cycle to cycle. In other portions of the same record the P waves disappear altogether and are replaced by "f" waves. Flutter-fibrillation is a term sometimes applied to these impure flutters which vary from moment to moment in their resemblance to flutter or fibrillation respectively.

Etiology. Auricular fibrillation occurs most commonly in cases of mitral stenosis (rheumatic heart disease), coronary arteriosclerotic heart disease with heart failure,[15] and hyperthyroidism.[25, 85] When established auricular fibrillation complicates hyperthyroidism there is often a simultaneous mitral stenosis or severe coronary disease (p. 920). Paroxysmal auricular fibrillation is particularly identified with hyperthyroidism although it is also associated with a variety of other conditions. Auricular fibrillation may occur in any type of heart disease, usually when there is congestive heart failure. This applies also

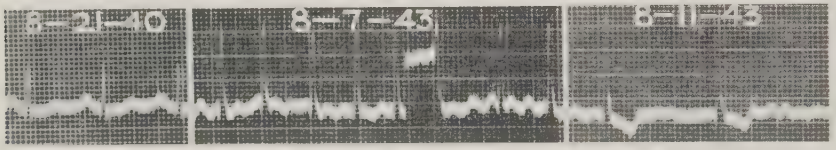


Fig. 34. Atrial fibrillation. 8/21/40 regular sinus rhythm. 8/7/43 atrial fibrillation. Irregular rapid ventricular rate, about 120 to 160. P waves absent. 8/11/43 patient digitalized. Atrial fibrillation persists, but ventricular rate is slowed to about 75 per minute. Coarse atrial fibrillary undulations but no distinct P waves.

to subacute bacterial endocarditis, in which the association of auricular fibrillation is not so uncommon as was formerly believed.[84] It is also not infrequent in the first two weeks after an acute myocardial infarction, when it appears as a paroxysmal occurrence which usually subsides spontaneously after several hours.

While auricular fibrillation is usually associated with severe organic heart disease, it is occasionally discovered in patients with apparently normal hearts in whom the arrhythmia is precipitated by some noncardiac condition. In particular, I have observed auricular fibrillation after surgical operations in the thorax, and also in the abdominal cavity, during pneumonia and less often with other infections, with pulmonary and mediastinal carcinoma and mediastinal lymphomata, after burns, with biliary and renal colic, and with visceral embolization and infarction, especially pulmonary embolization. In some of these conditions, I have strongly suspected the presence of underlying cardiac disease as a predisposing factor. In others there is direct invasion of the heart muscle by neoplasm or inflammatory tissue.

There are, however, also instances of purely functional auricular fibrillation without anatomic disease of the heart.[81] In some, tobacco, alcohol or other toxic factors appear to be precipitating or contributory causes. In others, fatigue, emotional stress, or violent exertions have been indicted, but there may be no apparent cause whatever. Rarely auricular fibrillation may be induced by carotid sinus pressure.[90] Familial occurrence has been re-

ported; [70, 131] I have observed two brothers with auricular fibrillation who were said to have had this condition paroxysmally since youth and for at least twenty years.

Paroxysmal auricular fibrillation may occur with any of the above conditions, but it is especially associated with hyperthyroidism (p. 920). The auricular fibrillation observed after thoracic surgical procedures, pneumonia, etc., is usually paroxysmal in character and of brief duration.

Auricular fibrillation occurs at any time between childhood and old age, but most frequently after forty.[85, 47] As might be anticipated, the average age of patients with auricular fibrillation and arteriosclerotic heart disease is about twenty years more than that of patients with rheumatic heart disease and this arrhythmia. The sex incidence in cases of auricular fibrillation is also conditioned by the underlying disease; females predominate in hyperthyroidism and mitral stenosis, males in coronary artery disease.

Symptoms. Symptoms referable to auricular fibrillation vary considerably and are often obscured by the symptoms of the associated cardiac or noncardiac disease. In paroxysms of auricular fibrillation or at the onset of permanent fibrillation, the ventricular rate is usually very rapid and the symptoms are those already described under paroxysmal tachycardia (p. 263). Most commonly there is palpitation, but there may also be precordial oppression or pain, anxiety or agitation and weakness or dizziness. The first paroxysm may announce itself by an attack of syncope. Symptoms of congestive failure or shock are apt to appear only if the tachycardia is very rapid (over 180) or if the attack is prolonged and the underlying cardiac disease has already greatly impaired myocardial reserve. However, congestive heart failure has been observed to result from uncontrolled auricular fibrillation in an otherwise normal heart.[14]

Established auricular fibrillation is usually better tolerated than the paroxysmal type, partly because the rate is slower and partly because the patient becomes adjusted to the disturbance. For these reasons the symptoms in established auricular fibrillation are usually those of heart failure and not of the arrhythmia. Occasionally, auricular fibrillation is discovered in patients who are completely unaware of any cardiac disorder. In some, auricular fibrillation is present on certain days and sinus rhythm at other times. Nevertheless there may be no detectable difference in the patient's sense of well-being. Asymptomatic auricular fibrillation with slow ventricular rate may become distressing if the ventricular rate becomes accelerated by exercise, emotional excitement, febrile disease or drugs. It is apparently the tachycardia rather than the ventricular irregularity that is chiefly and usually responsible for symptoms.

Certain *complications* may be precipitated by a paroxysm or at the onset of permanent auricular fibrillation.

1. *Heart failure* may be induced by the added burden of the irregular tachycardia on an already diseased heart. The heart failure induced in some instances of auricular tachycardia is usually rapidly reversible with spontaneous or induced restoration of sinus rhythm. But although the heart failure associated with auricular fibrillation may be controlled, it is usually chronic and requires continuous treatment thereafter.

2. *Auricular thrombosis* is favored by the occurrence of auricular fibrillation. For this reason auricular fibrillation is not infrequently a predisposing factor to cerebral, peripheral or visceral embolization and infarction. Sometimes

the emboli are dislodged when the auricular fibrillation reverts to normal rhythm spontaneously or after quinidine therapy. Very occasionally, in cases of mitral stenosis, the auricular thrombus formed after the onset of auricular fibrillation may continuously or intermittently obstruct the narrow mitral orifice (ball-valve thrombus) causing a shock-like picture and death (p. 576). Of course auricular thrombosis may occur in mitral stenosis even with sinus rhythm if there is left auricular dilatation. But it is probable that the absence of effective auricular contraction in auricular fibrillation favors thrombus formation. The detachment of such thrombi and consequent embolization may, however, occur as often in cases with sinus rhythm as with auricular fibrillation.

Signs. The distinctive physical sign is a complete irregularity of the heart beat. This is most readily ascertained at heart rates of 100 to 140. Regularity may be simulated when the ventricular rate is under 90 or over 150. The pulse also is completely irregular. At rapid ventricular rates, however, the pulse rate is usually considerably less than the apical rate; this difference is termed a pulse deficit. It results chiefly from failure of many of the weak ventricular beats to open the semilunar valves and expel the column of blood which produces the radial pulse. In part also the pulse deficit results from difficulty in counting weak pulse beats which are closely spaced. Because of the possibility of a pulse deficit, it is essential that the heart rate be determined by cardiac auscultation, especially when this is being used as a guide to treatment.

When treatment with digitalis has been instituted, the apical heart rate becomes slowed, the beats become stronger and more uniform in amplitude and the pulse deficit diminishes and then disappears. If the patient is first seen at this stage of digitalization, the heart and pulse rate may be found within a normal range of 70 to 80 and the heart and pulse may appear to be regular or almost so.

Heart Sounds. The second sound may be absent when the ventricular contractions, which occur after a brief diastole and incomplete filling, are too weak to open the semilunar valves. The first sound varies in loudness.[101a]

Other physical signs are determined by associated cardiac or noncardiac disease. Since mitral stenosis is the commonest underlying condition, enlargement of the left atrium, straightening or prominence of the pulmonary (left) border of the heart and an apical diastolic murmur may be observed. The typical presystolic rumble is usually absent or difficult to elicit in the presence of auricular fibrillation. If the heart rate is rapid, the diastolic murmur is sufficiently close to the first sound to simulate a presystolic murmur. When the heart rate is slow or the diastolic period is relatively long, there is an early diastolic murmur.

Diagnosis. For diagnosis and differential diagnosis of the tachycardias, see p. 288.

Course and Prognosis. Paroxysms of auricular fibrillation usually last for several hours or occasionally for a few days. When they persist for more than two weeks they usually are permanent unless specific treatment restores sinus rhythm. Paroxysms may occur infrequently or several times a week. Often a stage of paroxysmal auricular fibrillation precedes permanency of the arrhythmia. The persistence and recurrence of paroxysmal auricular fibrillation are usually determined by some underlying cause such as hyperthyroidism or mediastinal disease. The outlook then depends on the ability to discover and remedy the causative condition. Auricular fibrillation developing from several

days to two weeks after the onset of an acute myocardial infarction is almost always paroxysmal and of brief duration. Auricular fibrillation preceding or developing at the onset of the myocardial infarct usually persists. According to Brill,[13] 90 per cent of paroxysms of auricular fibrillation subside within a week but occasionally one may continue for as long as a year and yet cease spontaneously. On the other hand it is generally stated that once established, auricular fibrillation tends to persist permanently. Exceptions to this statement were reported by Burch,[18] who observed auricular fibrillation of twenty-two months' duration replaced by sinus rhythm, and by Fogel,[40] who observed spontaneous return to normal sinus rhythm after a purported duration of eleven years.

When paroxysmal auricular fibrillation occurs in a normal heart, it may be quite disturbing because of symptoms due to the tachycardia and because of the associated anxiety, but it is usually of no importance as regards the outlook for life or the development of heart disease.[129] When paroxysmal auricular fibrillation occurs in a diseased heart, the condition may be more serious because of the greater likelihood of precipitating congestive heart failure and the dangers of cerebral and peripheral ischemia.

As a rule the development of persistent auricular fibrillation is an unfavorable prognostic sign. In most instances it is associated with serious organic heart disease, and its occurrence usually denotes advanced disease with congestive heart failure in the offing if not already present. Persistent auricular fibrillation in patients with acute myocardial infarction is associated with a significantly higher mortality rate than in patients without this arrhythmia.[5] This may be a consequence of more extensive cardiac damage in the cases in which auricular fibrillation developed, rather than of the arrhythmia itself. Persistent auricular fibrillation in patients with hyperthyroidism is also a harbinger of early heart failure (p. 923). However the outlook in this disease is less serious because with the elimination of hyperthyroidism both the auricular fibrillation and heart failure usually disappear rapidly.

Aside from its unfavorable implications, established auricular fibrillation may itself contribute to an unfavorable prognosis. The effect of the rapid ventricular rate and the loss of effective auricular contraction in impairing cardiac function and inducing heart failure has been mentioned. On the other hand the finding of auricular fibrillation in a patient with heart failure may sometimes denote a better outlook than sinus rhythm and heart failure.[23] For if the auricular fibrillation is replaced by sinus rhythm after quinidine therapy or after thyroidectomy in cases of hyperthyroidism, the heart failure may likewise disappear. Or, if this is not possible, slowing of the rapid ventricular rate by digitalis and rest usually effects a striking improvement. These observations are applications of the general theorem that the outlook in heart failure is better if a causative factor can be found and eliminated than when there is no apparent, remediable cause.

Treatment. The treatment of auricular fibrillation depends somewhat on whether this arrhythmia is established or paroxysmal, and in the latter type whether an effort is being made to eliminate or to prevent the attacks. But treatment in all these circumstances consists essentially of the use of *digitalis* or *quinidine*. Treatment may be unnecessary if there are no symptoms due to the arrhythmia or if paroxysms subside spontaneously after a very brief duration and recur infrequently. In general, digitalis is indicated if there is evidence of circulatory insufficiency and preferred if there is significant underlying

cardiac disease even without heart failure. Quinidine is usually given first choice if the arrhythmia is a symptomatic disturbance, is of recent duration, and if there are no apparent heart disease, no significant cardiac enlargement and no heart failure. Quinidine is often employed when auricular fibrillation persists for more than a week after thyroidectomy for hyperthyroidism (p. 926).

Sometimes, despite the usual contraindication in cases with heart failure, quinidine may be employed with lifesaving effect after digitalis and other therapeutic measures have failed.[4] Similarly in patients with repeated embolization, with and without heart failure, quinidine has been given when the outlook was poor and has been effective not only in restoring sinus rhythm but also in terminating the embolization and improving the circulation.[92, 109, 124] When the ventricular rate is slow due to partial or complete heart block, quinidine is contraindicated.

Digitalis Therapy in Auricular Fibrillation. The *purpose* of digitalis therapy in auricular fibrillation is to slow the ventricular rate, not to restore sinus rhythm. As we have seen, most if not all of the circulatory disadvantages of auricular fibrillation are due not to the irregularity but to the rapid ventricular rate.

The *action* of digitalis in auricular fibrillation is essentially twofold: 1. By stimulating the vagus nerve it shortens the refractory period. This tends to perpetuate circus movements and therefore to foster auricular fibrillation by rendering the tissue responsive when the excitation wave completes its circuit. 2. By direct action on the a-v node and bundle, digitalis slows conduction. This prevents most of the excessive auricular impulses from reaching the ventricle, allows more time for ventricular diastolic recovery and filling, and results in slower, more forceful ventricular contractions. Thus the digitalis vagal effect tends to maintain the fibrillation of the auricles while the direct effect on the functional conduction system slows the ventricular rate. But the disadvantage of the former is more than compensated by the benefit of the latter.

The *dosage and methods of administering digitalis* have been described elsewhere in detail (p. 183). In occasional, very urgent situations it may be advisable to administer digitalis or ouabain intravenously. Rapid digitalization may also be accomplished by a single dose of digitoxin. The therapeutic effect and subsequent dosage should be gauged by the cardiac rate as determined by auscultation at the apex and not by examination of the pulse. Serial electrocardiograms are desirable but rarely essential. It is desirable to reduce the apical heart rate to between 60 and 70 per minute at rest. This may not be possible in the presence of complications or associated conditions causing fever, or in the presence of hyperthyroidism. After the desired ventricular rate is attained, the subsequent daily dose necessary to maintain this rate should be determined. In instances of persistent auricular fibrillation, it may be necessary to continue the maintenance dose of digitalis indefinitely.

The *toxic symptoms* of digitalis have been discussed elsewhere (p. 189). Attention is called again, in particular, to anorexia, nausea and vomiting, diarrhea, yellow vision, bigeminal rhythm, multifocal (bidirectional) premature ventricular contractions and heart block. Bradycardia of 50 or less or regular nodal rhythm developing during digitalis medication usually denotes excessive dosage.

Quinidine Therapy. The use of quinine for the treatment of cardiac irregularities was introduced in recent years by Wenckebach.[122] Quinidine, a

dextrorotatory isomer of quinine, was later introduced by Frey[42] and found to be more effective.

The *purpose* of quinidine therapy is to restore normal sinus rhythm. It is usually not preferred or is contraindicated in cases of chronic cardiac disease or heart failure, longstanding auricular fibrillation and cardiac enlargement because of the tendency of auricular fibrillation to recur when it is abolished, because of the danger of embolization from auricular thrombi as sinus rhythm is restored, and because of the risk of sudden death from cardiac standstill in patients with a-v or intraventricular block.

The *action* of quinidine in auricular fibrillation is as follows:

1. By direct action on the auricular musculature it prolongs the refractory period. Consequently, when the circus wave responsible for auricular fibrillation completes its circuit and finds the muscle still refractory, the circus movement is ended. This permits the sinoauricular node to reestablish itself as the pacemaker.

2. On the other hand quinidine also slows the rate of impulse transmission. This tends to perpetuate the circus movement by allowing the tissue before the crest of the excitation wave more time to recover from its refractoriness. If the first effect, above, predominates, quinidine may abolish auricular fibrillation. If the second predominates, auricular fibrillation persists. The second effect also tends to slow the auricular rate. Consequently auricular fibrillation is often converted to flutter before sinus rhythm is restored by quinidine.

3. Quinidine tends to increase the ventricular rate, but this undesirable temporary effect is negligible if sinus rhythm is restored. The increased ventricular rate results from (a) depression of the vagus nerve and therefore improved conduction of auricular impulses through the a-v node and bundle, and (b) the slowing of the auricular rate which allows better a-v conduction. The direct action of quinidine on the a-v bundle depresses conduction, but this action is more than overcome by (a) and (b).

Thus quinidine is employed primarily in the hope that it will restore sinus rhythm by prolonging the refractory period and thus abolish the auricular circus rhythm. On the other hand, digitalis is employed with a view to slowing the ventricular rate by depressing a-v conduction; its effect on the auricular fibrillation, if any, is to foster it by shortening the refractory period.

ADMINISTRATION OF QUINIDINE. One or two doses of 0.2 gm. (3 grains) each may be given an hour apart to test for sensitivity. This is done as a matter of custom; its value is uncertain. Subsequent dosage has not become standardized, since occasional patients experience a favorable response with one or two small doses while others require the maximal dosage that can be tolerated. As a rule I prescribe 0.3 gm. (5 grains) every two hours for six to eight doses, discontinuing when the patient is asleep at night. This dosage is repeated the following day if the arrhythmia persists. Thereafter if unsuccessful and if there are no toxic symptoms (see below, p. 281), I increase the dosage progressively and if necessary until 6 gm. daily (90 grains) is being administered. This is divided into twelve doses each of 0.5 gm. (7½ grains) every two hours, day and night. If this fails, it is rarely desirable or effective to exceed 6 gm. daily. When more than 2 gm. daily is given, serial electrocardiograms should be taken to observe whether excessive prolongation of intraventricular conduction occurs due to quinidine toxicity.

If normal sinus rhythm is restored at any point in this program, I discontinue the quinidine entirely, because often the sinus rhythm will persist despite interruption of the drug. If the arrhythmia recurs, I resume the effective dosage directly and gradually reduce it until I determine the minimal quantity required to maintain normal sinus rhythm. The same dosage program is usually followed whenever quinidine is employed in the treatment of any other disturbance in cardiac rhythm.

Many variations of the above schedule may be followed. In urgent cases quinidine may be given as often as once every hour, day and night. On the other hand, in most cases it is unnecessary to awaken the patient during the night and the drug may be given every four hours. In mild arrhythmias 0.3 gm. (5 grains) three or four times daily often suffices. Occasionally a single large daily dose is effective when multiple doses at regular intervals are not.[41] The peak of quinidine effect occurs earlier with larger doses and this may be important when rapid results are desired.[119]

Most physicians avoid the simultaneous administration of digitalis and quinidine because of a possibly dangerous potentiating effect, but there is no reliable clinical evidence to support this taboo. If quinidine is ineffective in restoring sinus rhythm, it may be discontinued and the patient digitalized in one, two or more days. Then the digitalis may be stopped for a day or two and another course of quinidine given. Actually, since the digitalis is not eliminated in one to two days (p. 180), it seems more logical to maintain digitalization and give quinidine another trial at the same time.[59, 5]

Very rarely the urgency of a situation may demand that quinidine be given parenterally, e. g., in some cases of ventricular tachycardia. Occasionally parenteral administration may be necessitated by the patient's inability to take drugs by mouth because of vomiting or by the uncertainty of absorption due to shock. *Quinine dihydrochloride,* 0.5 gm. or 7½ grains (marketed in ampules of 5 cc. containing 0.5 gm. of the drug for intravenous use), is administered very slowly until the desired effect is obtained or the entire contents are injected. *Quinidine lactate* is also supplied in ampules of 0.65 gm. dissolved in 10 cc. of sterile saline. The ampule's contents should be diluted with 50 cc. of 5 per cent sterile glucose solution and given intravenously at a rate of 3 to 5 cc. per minute. This dose may be repeated in two hours if necessary. *Quinidine sulfate* may be dissolved in distilled water or saline, 0.5 to 1 gm. being dissolved in 20 cc. distilled water and given slowly, or 4 gm. (60 grains) being dissolved in 500 cc. saline or 5 per cent glucose and administered by intravenous drip at the rate of 100 cc. per hour until the desired effect is obtained or toxic symptoms develop.[55] A soluble preparation of quinidine, containing 0.15 gm. (2½ grain) per cc., may be prepared for intramuscular injection according to the following formula:

	gm. or cc.
Quinidine hydrochloride	15
Antipyrine	15
Urea	20
Distilled water to make	100

The preparation is sterilized through a Berkefeld filter and then stored in ampules or rubber-capped vials. With this preparation injected intramuscularly Sturnick et al.[116] obtained a reversion to normal rhythm within three hours

in 15 of 21 attacks of ventricular tachycardia, auricular fibrillation or auricular tachycardia. The optimal initial dose was 0.45 to 0.6 gm. with a second injection if necessary after two to three hours.

Quinidine is a toxic and sometimes dangerous drug which must be administered with special care. It is therefore advisable that the patient be under close supervision. If large doses are given, serial electrocardiograms are desirable.

Among the *toxic symptoms* are those known as cinchonism, caused not only by the cinchona alkaloids, but also by salicylates and cinchophen. These symptoms, with mild intoxication, include tinnitus, impaired hearing, headache, nausea, mild diarrhea or a slight disturbance in vision. With more advanced toxicity, tinnitus and hearing impairment become more severe; there is blurring of vision, disturbed color perception, photophobia and diplopia (quinine amblyopia or amaurosis);[31] nausea, vomiting, diarrhea and abdominal pain are frequent; the skin becomes hot and flushed and urticarial, macular or papular eruptions occur; severe cerebral symptoms may develop ranging from headache to fever, confusion and delirium. I have observed a patient in whom a single dose of quinidine, given orally, was followed on several occasions by chills and fever within two hours and then by purpura and melena.

Respiratory distress, cyanosis, dizziness and cold sweat, sometimes of alarming nature, may result from quinidine idiosyncrasy.

A serious *tachycardia* associated with auricular flutter may follow treatment of auricular fibrillation by quinidine.[118] This is less likely to occur if quinidine is given after previous digitalization.

Intraventricular conduction defect with widening of the QRS to more than 0.12 second, cardiac standstill and ventricular fibrillation may result from the depressant effects of quinidine on the cardiac musculature and conduction system. Sudden death following quinidine therapy is more apt to be due to cardiac standstill (depression of the sinoauricular and a-v nodes) than to embolization.

All these symptoms and signs should be excluded by careful questioning and examination before each new dose of the drug is given. Serial electrocardiograms should be taken when large doses of quinidine are given or when the drug is administered for long periods. Occasionally mild symptoms may have to be tolerated if the arrhythmia is sufficiently disturbing and is controlled only by slightly toxic doses of quinidine. Otherwise the drug should be discontinued when symptoms of intoxication are discovered.

Restoration of sinus rhythm by quinidine has been observed in 50 to 88 per cent of properly selected and treated cases of auricular fibrillation.[109, 36, 87] Varied degrees of success are due to differences in dosage and especially to differences in the types of cases. Sinus rhythm once restored persists for a variable period, usually less than a year but occasionally for two to five years and sometimes longer.[94] Quinidine therapy may have to be continued indefinitely. Recurrence is most likely in cases with a progressive underlying cardiac disease or hyperthyroidism. In the former, it is advisable to discontinue quinidine and to digitalize the patient; in the latter the hyperthyroidism should be corrected.

Treatment of Paroxysms. Treatment of a paroxysm of auricular fibrillation is indicated only if it is associated with distressing and prolonged palpitation, evidences of heart failure or of cerebral or peripheral ischemia. Specific treatment is usually unnecessary when symptoms are mild or absent, when the

attack is of very brief duration or when it is symptomatic of some underlying disease such as hyperthyroidism, pneumonia, surgical procedures, etc. In the latter circumstances treatment is directed only to the underlying disease, for the arrhythmia subsides spontaneously or with cure of the basic cause.

When specific treatment of the arrhythmia is necessary, digitalis or quinidine or both are employed as described above for established auricular fibrillation. Quinidine is likely to have more frequent usage in paroxysmal than in established auricular fibrillation, while digitalis is usually preferred in established auricular fibrillation, since the latter is almost always associated with severe heart disease and often with heart failure. Digitalization may be attempted in those cases in which quinidine has failed and conversely quinidine may be used after digitalis has been administered first in an effort to slow the ventricular rate. (For dosage and methods of administration, see digitalis p. 183 and quinidine p. 279.) Atabrine (0.4 gm. intramuscularly) may be tried if these fail.[49]

Prevention of Attacks. Quinidine is usually employed to prevent attacks of auricular fibrillation which recur frequently and produce distressing symptoms. It is impractical to take this drug continuously when attacks occur rarely. When indicated the quinidine may be given in doses of 0.2 gm. (3 grains) three times daily and increased progressively in dosage and frequency until the attacks no longer recur, or symptoms of toxicity appear. But it is rarely justifiable to take more than a maximum of 4 gm. daily (divided in six to twelve doses). If the patient discovers that the attacks occur at definite times during the day or night or under special circumstances, a dose of quinidine sulfate, 0.2 to 0.4 gm. (3 to 6 grains), may be taken one to two hours prior to the time the attack is anticipated. Such extra doses at critical times may be used also to supplement the regular schedule of quinidine.

If quinidine proves ineffective in preventing frequent and annoying paroxysms, the patient should be digitalized (p. 183) and kept on maintenance doses of digitalis. This regime is designed, not to prevent attacks but to restrain the ventricular rate to below 100 per minute, if and when the attack should recur.

VENTRICULAR TACHYCARDIA

Ventricular tachycardia is a rapid, regular rhythm in response to stimuli arising in an ectopic focus or ring in the ventricular conduction system.[44] Usually the tachycardia occurs in brief paroxysms lasting minutes or hours, but occasionally it persists for weeks or months (Dubbs and Parmet,[32] 21 days; Freundlich,[41] 26 days; Mays,[83] 77 days). Gallavardin[45] has described a form of ventricular tachycardia recurring in very brief paroxysms, and characterized by runs of ventricular extrasystoles separated by one, two or several sinus beats.

Mechanism. The mechanism of ventricular tachycardia is probably similar to that of auricular tachycardia (p. 261), except that the ectopic focus or ring is situated in the ventricle instead of in the atrium. The tachycardia is then visualized as a series of rapid, rhythmic, premature beats arising in this ectopic focus or in response to a similar series of circus movements in a ventricular ring of tissue.[27]

Experimentally, ventricular tachycardia has been produced by ligation of a coronary artery, by the administration of barium chloride and by combined stimulation of the vagus and accelerator nerves.[101] Chloroform and cyclopro-

pane anesthesia predispose to the production of ventricular tachycardia by epinephrine.[69, 60, 1]

The ventricular rate varies usually between 150 and 250, but may be as rapid as 300 per minute. Sometimes the atria contract regularly and independently in response to the normal sinus impulse, while the ventricles respond to the ectopic ventricular stimulus. However, the atria may also respond to the ventricular stimulus which may be conducted backward (retrograde conduction) along the bundle branches, a-v bundle and node.[107] Since retrograde conduction is more difficult than normal downward conduction along the bundle and since the rate of ventricular impulse formation is excessive, various degrees of ventricular-auricular block may occur. In this respect ventricular tachycardia resembles auricular flutter with a reversal in origin and direction

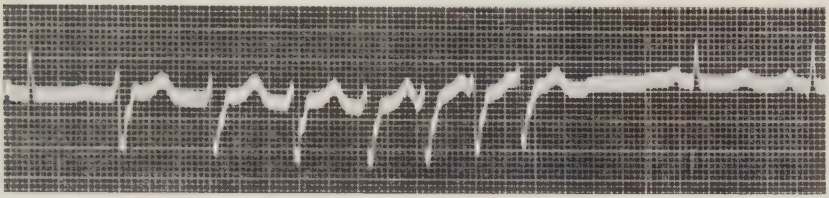


Fig. 35. Paroxysmal ventricular tachycardia. Lead I. A brief paroxysm preceded and followed by sinus beats. Abnormal configuration QRS complexes denoting ectopic focus but all from same site. Slower rate and slight irregularity of R-R cycles in contrast with regularity in auricular tachycardia.

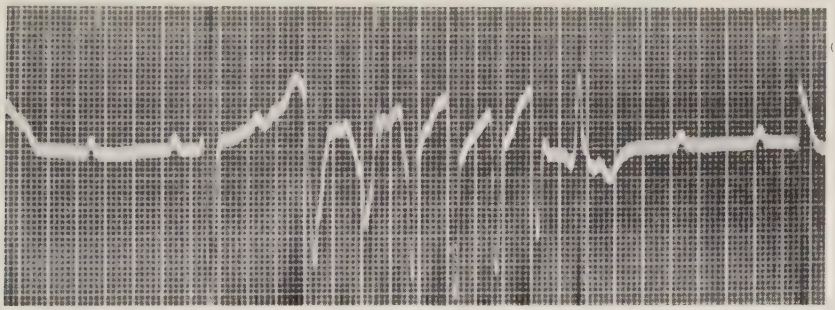


Fig. 36. Ventricular tachycardia in complete heart block associated with Adams-Stokes syndrome. Attacks accentuated by administration of epinephrine.

of the controlling impulse. In fact ventricular tachycardia is sometimes used synonymously with ventricular flutter.

The Electrocardiogram. The electrocardiogram of ventricular tachycardia is characterized by (Figs. 35, 36):

1. *QRS complexes with approximately regular rhythm, which are slurred and widened, at rates of 150 to 200 or more per minute.* The configuration of the QRS is that of a left or right ventricular premature beat, or the complexes may be alternatingly bidirectional. The latter is most often associated with digitalis intoxication[38, 136] and severe myocardial damage. The change in direction has been attributed to cardiac control by two independent ventricular foci[136] or to a single ectopic impulse, possibly at the bifurcation of the bundle of His, which is transmitted alternately over the left and right bundle branches because of a defect in conduction.[103]

2. The P waves are usually undisturbed in their sinus rhythm, but are often obscured by the ventricular complexes. Esophageal or right precordial leads may disclose the P waves at a slower rate than ventricular systoles. When retrograde conduction occurs, the P waves may be observed, abnormal in contour, and superimposed on the T waves or following them. Occasional P waves may be missing due to retrograde partial heart block (dropped auricular beats).

Occasionally auricular fibrillation or auricular tachycardia accompanies paroxysmal ventricular tachycardia.

Following subsidence of the tachycardia the T waves may be inverted for a few hours or days, possibly due to myocardial fatigue or ischemia occasioned by the tachycardia.[20, 111] The electrocardiographic pattern seen after a paroxysm of ventricular tachycardia may closely simulate that of acute myocardial infarction.[48, 41, 33] This similarity is heightened when the paroxysmal tachycardia is accompanied by intense precordial oppression or pain. The differentiation can usually be made by a consideration of the history and ancillary clinical findings (Chapter 21).

Occasionally the electrocardiogram of ventricular tachycardia may be confused with that of auricular tachycardia and intraventricular conduction disturbance, or with auricular flutter and 1:1 block. Ventricular tachycardia may be distinguished in a long strip of the electrocardiogram by the finding of isolated premature ventricular beats with the same QRS configuration before or after the paroxysm, or by the discovery of P waves in abnormal relationship to the QRS complex.

Etiology. Paroxysmal ventricular tachycardia is most often associated with recent myocardial infarction, but it may occur also with hypertensive and arteriosclerotic heart disease or after excessive amounts of digitalis.[128] Wilson et al.[130] described a clinical type of ventricular tachycardia, apparently induced by exertion. Occasionally ventricular tachycardia is observed to occur without obvious cause in persons without evidence of organic heart disease.[86, 41, 76]

Symptoms and Signs. The subjective symptoms are identical with those described under auricular paroxysmal tachycardia (p. 263). Essentially these are attacks of palpitation, starting and stopping suddenly, lasting from a few minutes to many hours, and associated occasionally with symptoms of congestive heart failure or with dizziness, faintness or syncope due to cerebral ischemia caused by a deficient cardiac output. Occasionally there is little or no subjective distress even when, as in a case described by Freundlich,[41] the tachycardia persisted for 26 days.

Examination discloses an apical and pulse rate of 160 to 180, but occasionally as high as 200 to 300 per minute. Although the rhythm is regular, prolonged auscultation of the heart may disclose slight irregularity as well as corresponding differences in the quality or intensity of the first sound.[114] (But see also MacKinnon.[78]) The latter is due to varying relationships of the auricular and ventricular contractions in different cycles and therefore to differences in the position of the atrioventricular valve cusps which determine the character of the first heart sound.

The jugular veins may, as in auricular tachycardia, show prominent regurgitation ("a") waves due to the occurrence of auricular contraction, while the tricuspid valve is closed by simultaneous ventricular systole. There are fewer jugular pulsations than apical heart beats.

Other symptoms and signs often present are due to an underlying acute myocardial infarction, to digitalis intoxication, or to the heart failure which necessitated the use of digitalis.

Diagnosis. For diagnosis and differential diagnosis of the tachycardias, see p. 288.

Prognosis. Ventricular tachycardia, unlike auricular tachycardia, is usually a serious condition, partly because of the frequency of an underlying myocardial infarction and partly because it may be the harbinger of a fatal ventricular fibrillation. Ventricular tachycardia with alternating direction of the ventricular complexes has been considered especially ominous and almost invariably fatal. But recoveries have been observed with appropriate treatment whether the direction was unidirectional or bidirectional.[12, 41] Zimmerman[137] treated 8 of 10 cases of ventricular tachycardia with quinidine, with recovery in 7 of them. In general, the prognosis of ventricular tachycardia, as of most arrhythmias, depends on the absence or presence of underlying cardiac disease and on the outlook presented by that disease.

Treatment. Quinidine effectively restores normal rhythm in the majority of cases, possibly by abolishing a circus movement as in auricular fibrillation (p. 279). Various dosages and modes of administration have been recommended.[68, 3, 41] Oral administration is preferred except in extreme emergency; the dosage is that which accomplishes the desired result. After giving a test dose of 0.2 gm. (3 grains), one may follow the dosage schedule described under auricular fibrillation (p. 279). Maintenance doses, varying from 0.3 gm. (5 grains) two or three times daily to 1 gm. or more five times daily, may be required for several days or longer to prevent a recurrence. Rarely intravenous or intramuscular injections of quinine dihydrochloride or quinidine lactate (p. 280) may be necessary in extreme emergency, or if the patient is vomiting.[98, 32] Frequent electrocardiograms are desirable to avoid toxic effects and to evaluate the effectiveness of quinidine therapy.

Other measures have been successfully employed to stop attacks of ventricular (and auricular) paroxysmal tachycardia. *Magnesium sulfate* in 20 per cent solution may be given intravenously, the first 5 cc. very slowly and then an additional 5 to 10 cc. if there are no ill effects and if the arrhythmia persists.[138] *Calcium chloride* or *gluconate* has been reported to be effective when given intravenously in 10 per cent solution (10 to 20 cc. equals 1 to 2 gm.). *Potassium salts* (the chloride, acetate or iodide) have been given orally in doses of 1 to 5 gm. (15 to 75 grains) two to six times daily to decrease the frequency of attacks.[102, 112] In one case, in which the arrhythmia failed to respond to all of the above measures, sinus rhythm was restored and heart failure eliminated following the intramuscular injection of 0.4 gm. of atabrine. The intravenous injection of 10 to 40 mg. of morphine sulfate, repeated if necessary in a half to two hours, has been advocated.[57] In contrast with its usefulness in the treatment or prophylaxis of auricular paroxysmal tachycardia, digitalis may be dangerous in cases of ventricular tachycardia.

VENTRICULAR FIBRILLATION

Ventricular fibrillation is an extreme arrhythmia characterized by rapid, irregular, uncoordinated and ineffective twitchings of the ventricles.

In animals ventricular fibrillation may be induced by electrical stimulation (faradization), as was first demonstrated in Ludwig's laboratory in 1850.[61]

But it may also be induced experimentally by coronary artery ligation, mechanical irritation, drugs such as barium chloride, calcium chloride, digitalis or epinephrine in excessive dosage. Chloroform and cyclopropane anesthesia are predisposing factors. It will be noted that many of these factors have been mentioned as capable of producing ventricular tachycardia. In fact ventricular premature beats, ventricular tachycardia and ventricular fibrillation are not an uncommon sequence in both experimental and human fibrillation of the ventricles.

Mechanism. The responsible mechanism, as in auricular fibrillation, is probably an irregular or inconstant circus movement. According to Wiggers,[125] fibrillation starts with a premature beat from an ectopic focus or ring in the ventricle, and is followed by circus movements involving smaller and smaller rings of myocardium, each of which develops independent excitations. This produces relatively ineffectual fractionate muscular contractions which become weaker and weaker as the coronary blood flow diminishes. The circulatory

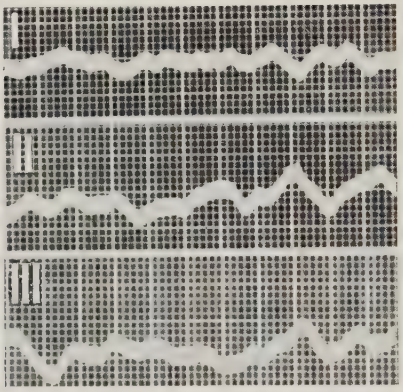


Fig. 37. Ventricular fibrillation in a fatal paroxysm of Adams-Stokes syndrome.

effects of ventricular fibrillation are much more serious than those of auricular fibrillation, for cardiac contraction becomes so ineffective that it is tantamount to asystole. The stroke output is annihilated and syncope and death follow.

The Electrocardiogram. The electrocardiogram exhibits rapid, regular or irregular oscillations representing bizarre QRS complexes (Fig. 37). One type of oscillation is fairly uniform with an amplitude of 8 to 10 mm. and a frequency of 130 to 300 per minute, which may gradually diminish as asphyxia develops.[105] This type has no isoelectric interval and is sometimes called ventricular flutter. In a second type the oscillations are irregular, somewhat more rapid and vary in amplitude (from 3 to 18 mm.), width and configuration. Terminally, ventricular fibrillation is characterized by completely irregular waves of low voltage or mere irregular undulations. There is usually complete or partial heart block and established a-v dissociation, or there may be sinus rhythm. In any event the auricles continue their regular rhythm and usual rate until asphyxia develops.

The attack of ventricular fibrillation is usually introduced by an acceleration of the basic ventricular rhythm, always by "initial" premature beats, and often by short runs of irregular ventricular oscillations.[106] During the attacks

there may be short or long asystolic pauses followed by a recurrence of the irregular rhythm of fibrillation or a return to the dominant rhythm (usually sinus rhythm with heart block), with occasional ventricular premature beats.

Etiology. In humans ventricular fibrillation may occur following acute cardiac infarction, during surgical procedures under general anesthesia, following electrocution or lightning shock, after toxic doses of digitalis or quinidine, or as a terminal event in a variety of diseases, usually after a more or less brief period of ventricular tachycardia. Since ventricular fibrillation is discovered accidentally and only by means of the electrocardiograph, it is uncertain how many unexplained and sudden deaths result from ventricular fibrillation.[80, 115] Although the available experimental and clinical observations indicate that myocardial anoxia or necrosis[127, 52] or certain toxic disturbances are chiefly responsible for initiating ventricular fibrillation, the exact mechanism is uncertain.

Clinical Aspects. Ventricular fibrillation is usually viewed as a terminal and terminating incident in certain instances of sudden death, e. g., during an attack of angina pectoris or acute coronary occlusion; in syphilitic aortitis; after the intravenous injection of drugs such as strophanthin; after electrical contact; during anesthesia, etc., in all of which there may be insufficient anatomic change to account for the fatality. Ventricular fibrillation may also occur as a terminal incident in diseases which in themselves represent adequate causes of death.

Of more practical importance are the cases in which ventricular fibrillation is not soon fatal but occurs in transient paroxysms from which the patient recovers for a variable period of time. I have seen several patients suffer such attacks over a period of months, while another experienced innumerable ones over a period of forty-eight hours. Recovery may occur after absence of the heart beat for as long as five minutes.

These paroxysms are exhibited clinically as attacks of Adams-Stokes syndrome (p. 302), with syncope and convulsions indistinguishable from those due to ventricular standstill.[106, 96, 97] The fruitless ventricular twitches without mechanical expulsion of blood result in periods of asystole which are identical in effect with those due to ventricular standstill. Faintness occurs when ventricular fibrillation lasts 3 seconds or more, syncope after 10 to 20 seconds and convulsions, apnea and incontinence after 40 seconds (average figures).

The distinction (by the electrocardiograph) between Adams-Stokes attacks due to ventricular fibrillation and those due to ventricular standstill is important because epinephrine, ephedrine and other sympathomimetic drugs which are useful in the management of paroxysms due to ventricular standstill may be dangerous in those due to ventricular fibrillation.

Treatment. The treatment of syncopal and epileptiform attacks due to ventricular fibrillation consists of the administration of quinidine in increasing doses until there is definite toxicity or until the attacks are controlled (p. 279 for dosage and administration[67]). Quinidine has also been recommended as a routine measure in all patients with acute myocardial infarction in the hope of preventing ventricular tachycardia and ventricular fibrillation. The intravenous administration of a coronary vasodilator such as aminophylline (p. 491) and oxygen therapy may be tried when the attacks of ventricular fibrillation occur in patients suffering from severe coronary disease.

Both mecholyl[90] and papaverine[77] have been shown to have a preventive effect in experimental ventricular fibrillation, but their value in human cases has not been demonstrated. Wiggers[125] has abolished ventricular fibrillation in

dogs by passing strong alternating currents momentarily through the ventricles ("serial defibrillation"), and Beck and his associates[8] reported the cure of operative ventricular fibrillation of at least ten minutes' duration in a fourteen year old boy, by means of series of electric shocks.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF TACHYCARDIAS

The tachycardias may first be segregated according to whether the rhythm is regular or irregular. If regular, the tachycardia may be sinus tachycardia, auricular or ventricular paroxysmal tachycardia or auricular flutter. A sudden onset and cessation of palpitation and tachycardia and the history of similar paroxysms is characteristic of the paroxysmal tachycardias and flutter, but not of sinus tachycardia. If the heart rate exceeds 160, and especially if it is between 180 and 200 per minute, the disorder is usually a paroxysmal tachycardia, most commonly auricular. Sinus tachycardia and auricular flutter are associated with rates below 160 per minute, although the latter in infants may exceed 250 per minute. Tachycardias occurring in paroxysms lasting beyond a week are much more likely to be due to auricular flutter than to auricular paroxysmal tachycardia.

Sinus tachycardia differs from paroxysmal tachycardia in that it does not start or stop suddenly; the heart rate accelerates gradually, e. g. from 80 to 100, 120, 140 per minute, and similarly subsides gradually instead of in a few beats as do the paroxysmal tachycardias. Furthermore, the cardiac rate in sinus tachycardia varies from minute to minute, especially with change of posture and exercise, and occasionally with respiration. The heart rate in paroxysmal tachycardia persists with almost mathematical constancy (allowing a maximal variation of 2 beats per minute for difficulty in counting), despite posture, exercise or respiration. Auricular flutter may disclose equal constancy in cardiac rate, but occasionally there are sharp arithmetic divisions in rate due to heart block, e. g., the rate may be reduced to one-half its previous rate. With exercise, the ventricular rate in auricular flutter may increase in some arithmetical ratio, e. g. from 150 to 200 due to a change from 3:1 to 2:1 block, whereas the increase in rate following exercise is much more gradually progressive in cases of sinus tachycardia.

Carotid sinus pressure is often of great value in differential diagnosis as well as in treatment. *Sinus tachycardia* may not alter or it may respond with slight gradual slowing followed by a rapid return to the previous rate. *Auricular paroxysmal tachycardia* is usually suddenly reverted to normal sinus rhythm after a very brief pause or a few ventricular extrasystoles; occasionally there is no effect. *Ventricular tachycardia* is not modified at all. *Auricular flutter* may be slightly and temporarily slowed or there may be a sharp reduction in rate due to induced heart block, but sinus rhythm is not restored as it is in auricular tachycardia. Slowing of the heart rate by carotid sinus pressure may also be useful when combined with electrocardiography, using a lead from the third interspace to the right of the sternum.[34] This slowing may reveal P waves previously obscured in T or QRS complexes and thus demonstrate auricular flutter with 2:1 block, independent atrial rhythm in paroxysmal ventricular tachycardia or a-v nodal rhythm which was confused with auricular fibrillation or complete heart block.

Inspection of the cervical veins is occasionally helpful in differential diag-

nosis. Sinus tachycardia is associated with the normal "a," "c," "v" waves and the characteristic systolic collapse. In cases of auricular tachycardia the cervical veins may be prominent but not distinctive. On the other hand ventricular tachycardia may be distinguished by the greater frequency of the heart rate as compared with the prominent jugular "a" pulsations due to retrograde v-a block. Auricular flutter may be diagnosed by the presence of characteristic rapid flutter "a" waves which are usually more frequent (2:1) than the heart rate.

The *heart sounds* may help to distinguish ventricular tachycardia, for there is sometimes a recurrent variation in the quality or intensity of the first sounds. Furthermore, although the rate is persistently regular as in auricular tachycardia, the regularity is not as mathematically constant in ventricular tachycardia. When listening for several minutes one may discover slight disturbances in the regularity of the heart beat. In auricular flutter, audible auricular contractions may be of differential diagnostic value.

If the tachycardia is irregular, the arrhythmia is usually auricular fibrillation if the heart rate exceeds 130 per minute. Below this rate the irregular rhythm may be due to numerous premature beats with sinus tachycardia. Auricular flutter is occasionally irregular when there are dropped beats due to heart block or variations in the degree of block. The rate may then be rapid or slow. Differentiation of the various irregular tachycardias is aided by artificial increase of the heart rate to 140 or more with exercise, amyl nitrite or atropine. This accentuates the irregularity if due to auricular fibrillation, while that due to premature beats disappears. The same procedure may be useful when there is uncertainty as to the presence of auricular fibrillation with normal or slow ventricular rates, due to seeming regularity of the pulse. It also differentiates this slow ventricular type of auricular fibrillation from cardiac irregularity due to sinus arrhythmia. However, exercise will not induce an irregularity when auricular fibrillation is associated with complete heart block and the ventricles are really beating regularly with their idioventricular rhythm, or when the a-v node becomes the pacemaker of the ventricles (a-v dissociation) due to digitalis intoxication.

Finally differentiation depends on and is made most certainly by a study of electrocardiograms, the findings in which are discussed in detail under the individual headings.

It is worthy of note that oppression of the chest or severe pain may so dominate the clinical picture of a paroxysmal tachycardia that it is mistaken for an acute myocardial infarction. Occasionally this difficulty is enhanced by the association with the pain of weakness, fall in blood pressure and pulse pressure and rarely of mild fever and leukocytosis. However, a careful history discloses that the onset was dominated by the tachycardia and palpitation and that the intense thoracic oppression or pain and the circulatory disturbances occurred secondarily. Conversely paroxysmal tachycardias may develop after an acute coronary occlusion, but they appear days after the basic clinical manifestations of acute myocardial infarction. Sometimes the circulatory disturbances incidental to a severe and prolonged paroxysm of auricular tachycardia may induce myocardial infarction in patients with severe coronary arteriosclerosis and deficient coronary reserve.

From the diagnostic viewpoint it is appropriate to recall that the observation of paroxysmal auricular fibrillation should suggest a search for hyperthyroidism

or less likely for mediastinal disease. In cases of established auricular fibrillation without apparent cause, one should consider the possibility of having overlooked an underlying mitral stenosis or "masked" hyperthyroidism.

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13

DISTURBANCES IN CONDUCTION: HEART BLOCK AND BUNDLE BRANCH BLOCK

The disturbances in conduction, known as heart block, may be classified as:

1. Sinoauricular block.
2. Auriculoventricular block.
3. Bundle branch block including intraventricular block.
4. Short P-R interval with prolonged QRS complex.

SINOAURICULAR BLOCK

Sinoauricular block is a disturbance in which the auricular response is delayed or omitted because of partial or complete interference with the propaga-

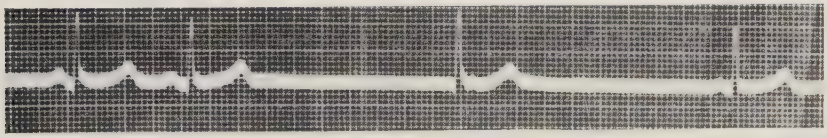


Fig. 38. Sinoauricular block in woman, aged 57, with diabetes and coronary artery disease. Pauses approximately equal to two normal intervals in long strips. After the first pause there is a nodal beat.

tion of impulses from the sinoauricular node to the atria.[95] Experimentally such block has been produced and demonstrated by isolating the s-a node through ligation and recording simultaneously the activity of the s-a node and other parts of the atria.[23] Despite regular sinus impulse formation there is no response of either atria or ventricles because the impulse cannot reach these structures. In clinical experience such sinoauricular block cannot be distinguished from sinus arrest or sinoauricular standstill (p. 242), in which there is a failure of sinus impulse formation.

Electrocardiographically, sinoauricular block is characterized by a pause, during which a P wave and its accompanying QRST complex are lost (Fig. 38). The P-P interval is twice or almost twice the dominant P-P interval. Occasionally the block persists over two, three or more cycles, and the P-P pause is correspondingly prolonged. The pauses may not be exact multiples of a normal P-P interval because, as in all disturbances of the sinoauricular node,

there may be an associated sinus arrhythmia, and because the sinoauricular conduction time may vary from beat to beat just as the a-v conduction may vary in a-v heart block.

There may be recurrent sinoauricular block in which there is an interruption of alternate sinus impulses (2:1 sinoauricular block). The auricular rate becomes halved, e. g. from 76 to 38 per minute, and secondarily of course the ventricular rate is likewise halved. This simulates sinus bradycardia electrocardiographically, and auriculoventricular heart block clinically. If the sinoauricular block leads to a complete absence of auricular response, the condition is termed auricular standstill (p. 242). In this condition auricular contractions disappear for a long or short period, while the ventricle responds to impulses from the a-v node, which becomes the pacemaker of the heart (a-v nodal escaped beats or nodal rhythm). An analogy is sometimes made with auriculoventricular block, viz.: (1) isolated auricular pauses (partial sinoauricular block) corresponding to partial a-v heart block with dropped beats; (2) recurrent auricular pauses every second beat or third beat, etc. (high grade but incomplete 2:1, 3:1 sinoauricular block), corresponding to incomplete 2:1, 3:1, etc., a-v block; and (3) auricular standstill with ventricular response to a-v node or idioventricular center (complete sinoauricular block) corresponding to complete a-v block with idioventricular rhythm. Occasionally, prolonged auricular standstill develops without the appearance of an a-v nodal or other idioventricular pacemaker; in consequence Adams-Stokes attacks may occur because of prolonged ventricular standstill. As a rule, however, after the dropping of a few beats, an a-v nodal beat escapes, or with more complete sinoauricular block a-v rhythm develops. Electrocardiograms of sinoauricular block may have a bizarre appearance due to the intrusion of escape (a-v nodal) beats, and the appearance of unconducted normal auricular contractions (P waves without following QRS) due to their precocious development after the escape beat and while the ventricle is still refractory. (See interference dissociation, p. 246.)

There is a frequent association of a-v block with sinoauricular block. The former may be denoted by prolonged and varying P-R intervals or there may be complete heart block (p. 297). The sinoauricular block may appear occasionally in a case of permanent complete heart block,[43] or sinoauricular block may lead to almost complete auriculoventricular dissociation without primary a-v block.[91]

Etiology. Sinoauricular block usually results from sensitivity to or intoxication by digitalis and occasionally quinidine. It may also be caused by vagal stimulation due to a sensitive carotid sinus, tumors compressing the carotid sinus, vagal reflexes during anesthesia and surgical procedures, or because of cerebral lesions. The reported occurrence of sinoauricular block with deep inspiration and its disappearance after the administration of atropine also support the causal importance of vagal influence. According to Kisch and Zucker,[43] sinoauricular block is never a physiologic phenomenon, but is due to several factors acting together, e. g., myofibrosis in the region of the s-a node, increased vagal tone and coronary insufficiency. Sinoauricular block may be observed in the course of acute infections, such as diphtheria, pertussis, mumps.[85] It is also possible that sinoauricular block is due rarely to organic lesions in the neighborhood of the sinoauricular node, e. g. following auricular infarction.

Clinical Aspects. Sinoauricular block occurs much more rarely than auriculoventricular block. It is usually of no clinical importance, but with long or frequent pauses in the heart beat the patient may experience dizziness, faintness or even attacks of the Adams-Stokes syndrome (p. 302). Death may occur when there is prolonged cardiac standstill.

Differential Diagnosis. Sinoauricular block may have to be distinguished from sinus bradycardia and from auriculoventricular block. The electrocardiogram is usually distinctive. Clinically auriculoventricular block may be distinguished from sinoauricular block by the finding of auricular "a" waves in the cervical veins during the pause in heart sounds in the former. Auricular "a" waves are absent in the pauses due to sinoauricular block.

Treatment. Treatment is rarely necessary since there are usually no symptoms. When sinoauricular block is due to digitalis or quinidine, these drugs should be stopped. If attacks of dizziness or syncope occur, atropine, 0.6 mg. to 1.0 mg. (1/100 to 1/60 grain) may be given subcutaneously and repeated after two to four hours as needed and tolerated. Ephedrine, 25 mg. (3/8 grain) every four to eight hours as tolerated, may also be useful.

In an emergency due to cardiac standstill which results from sinus arrest or sinoauricular block the administration of 0.5 to 1 cc. of 1:1000 solution of epinephrine, subcutaneously, intravenously or intracardiac may be lifesaving.

AURICULOVENTRICULAR BLOCK

Auriculoventricular block is the cardiac mechanism resulting from defective conduction of the impulse from atrium to ventricle. There may be merely a delay in transmission of the impulse through the a-v node and bundle, or there may be a complete interruption of occasional or of all impulses. Accordingly, auriculoventricular block is classified as:

1. Prolonged auriculoventricular conduction time (first degree block).
2. Partial heart block (second degree block).
3. Complete heart block (third degree block).

Heart block may be transient or permanent and it may represent a functional or organic disturbance. Complete heart block may appear in recurrent attacks with normal conduction between attacks.[12, 14, 48] Heart block is one of the commoner disorders of the heart beat. Its incidence is uncertain because the lesser degrees of heart block are mostly overlooked. However, it is probable that heart block is exceeded in frequency only by premature beats, auricular fibrillation and paroxysmal auricular tachycardia. Prolonged a-v conduction time, partial heart block and complete heart block are encountered in that order of frequency.

Mechanism. Experimentally, auriculoventricular block can be produced by cutting, ligating, clamping or otherwise injuring the a-v bundle (of His).[22] Ligation or artificial embolization of the coronary arteries, the application of destructive chemicals or cold, drugs such as morphine, epinephrine or digitalis,[92] diphtheria toxin, asphyxia,[53] and vagal stimulation (especially of the left vagus[81]) have been employed to cause heart block experimentally. The toxic agents produce heart block either by direct action on the conduction tissue or indirectly through vagal stimulation or both. It has been shown that the most susceptible site, i. e. the site responsible for the block, is the upper portion of the auriculoventricular node.

If the bundle is only partially divided, with varying degrees of completeness,

or if progressive degrees of compression are applied, various stages of heart block are induced: (1) The sinoauricular impulses may all traverse the a-v node and bundle and cause a ventricular response, but the delay in conductivity results in a prolonged auriculoventricular (or P-R) interval. (2) Occasional sinus impulses cause auricular contractions but are not followed by a ventricular response. (3) There is a regular sequence of dropped beats, with an auriculoventricular ratio of 8:7, 5:4, or 4:3, etc. Or the ventricle responds to every second, third or fourth auricular contraction resulting in 2:1, 3:1 or 4:1 block. (4) Finally, with complete block, none of the auricular impulses reach the ventricles. However, the ventricles continue to beat independently of the atria (a-v dissociation) in response to a pacemaker in the a-v bundle below the site of block or rarely in response to a pacemaker in the ventricular musculature (idioventricular rhythm). If at the onset of complete heart block a new pacemaker fails to appear, ventricular standstill occurs.

The Electrocardiogram. *1. Prolonged Auriculoventricular Conduction Time.* The P-R interval exceeds 0.2 second (Fig. 39). It may be as long as 0.3 second and occasionally 0.5 second or more. As a rule every P wave is followed by a QRST complex and the waves are normal in configuration. In such instances

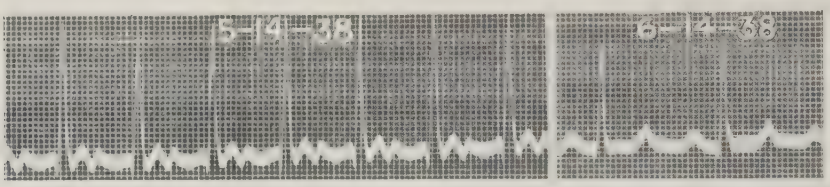


Fig. 39. Atrioventricular block in rheumatic fever. Lead II. May 14, P-R interval prolonged to 0.28 during rheumatic activity. June 14, ventricular rate slowed but P-R interval still prolonged.

the rhythm of the heart is regular and the prolongation of a-v conduction is betrayed only by the electrocardiogram. However, delayed auriculoventricular conduction may be combined with more severe degrees of a-v block. When the P-R interval exceeds 0.3 second, there are usually occasional dropped beats which result in some irregularity.

Normally the P-R interval varies between 0.12 and 0.2 second. At slow cardiac rates (60 per minute or less) a P-R interval up to 0.21 or 0.22 may be normal. P-R intervals exceeding 0.2 second and up to 0.28 second were found in 16 of 1000 young, apparently healthy aviators.[27] With very long P-R intervals or with rapid rates, the P-R interval may be difficult to measure because the P wave becomes obscured by the preceding T or QRS complex. The presence of a very high or deformed T wave often suggests fusion with the following P wave.

2. Partial Heart Block (Second Degree Block). There are various grades of partial heart block according to the frequency with which auricular impulses are not followed by ventricular contractions.

(a) Periodically there is a dropped beat. For example there may be seven P waves followed regularly by QRST complexes, while the eighth P wave has no subsequent ventricular complex. If the ninth P wave and corresponding ventricular complex follow at their regular interval, the mechanism would be termed an 8:7 block, denoting 7 ventricular responses to 8 auricular beats. The contours of the various waves are unaltered.

(b) Occasionally the P-R interval increases progressively until a QRS complex falls out. Following this, the P-R interval becomes smaller, but thereafter again increases progressively until there is another dropped beat, and seriatim. This has been termed the Wenckebach phenomenon and the increasing intervals between beats are called Wenckebach periods (Fig. 40). It is believed that the progressive delay in conduction denotes increasing fatigue of the a-v node or bundle, until it is incapable of conducting an impulse at all. With the rest period occasioned by the dropped beat, the bundle recovers partially, the P-R interval is somewhat shorter but again with each conducted impulse the speed of conduction becomes impaired. In this type of partial

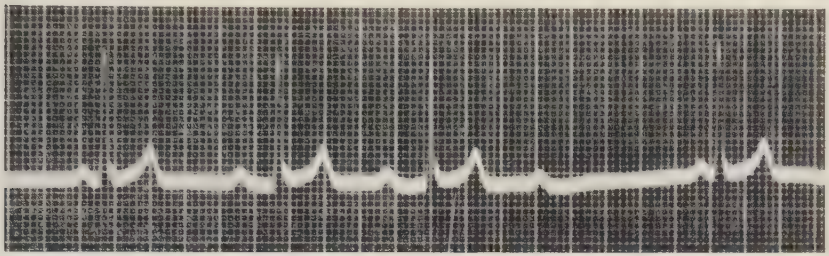


Fig. 40. Atrioventricular block with Wenckebach periods. Lead II. Progressive prolongation of P-R interval until after fourth P wave a beat is blocked. P-R interval after pause is shortened.

heart block, the ventricular rhythm is irregular, partly because of the changing P-R interval and partly because of the dropped beats.

(c) With more severe partial heart block the ventricles respond only to every second, third or fourth beat, resulting in 2:1, 3:1 or 4:1 block (Fig. 41). This is indicated by QRST complexes following every second, third or fourth P wave, but not the intermediate P waves. The ventricular rate is usually regular and may be slow if the auricular rate is normal. However, the ventricular rate may be rapid, e. g., 150 per minute in cases of auricular flutter with auricular rates of 300 per minute and a 2:1 heart block. At times there is a dominant degree of block, e. g., 3:1 with variations from 2:1 to 4:1. In such cases there



Fig. 41. Incomplete heart block 3:1. Lead II. There is a ventricular response to every third sinus impulse and the P-R interval is constant.

may be an irregularity in the ventricular rate. 2:1 block is the commonest ratio observed, but alternating cycles of 2:1 and 1:1 or of 2:1 and 3:1 are not uncommon.

3. Complete Heart Block. The essential electrocardiographic feature of complete heart block is the virtual regularity of atrial and ventricular activity with continual variation in the P-R interval (Fig. 42). The auricular rate is higher than the ventricular rate, i. e., there are more P waves than QRS complexes. But both the auricular and the ventricular rhythms are essentially regular. As a rule the auricular rate is 70 to 80 per minute (normal), while the ventricular rate is 30 to 40 or half as great. This simulates but should not be

confused with 2:1 block, for in 2:1 partial heart block the QRS complexes follow every second P wave after a constant interval.

The QRS complexes bear no constant time relationship to the P waves. Any attempt to measure a "P-R interval" discloses irregular variations. The QRST complex represents a response to a pacemaker in the a-v junctional tissue or in the ventricles, while the P wave denotes excitation by the sinoauricular node. There is therefore an auriculoventricular dissociation in complete heart block. Occasionally P waves recur regularly while there is a variable period without QRS complexes (ventricular asystole) (Fig. 43).

The QRS complexes in complete heart block[37] are usually of normal configuration, although slight distinctive modifications are observed intermittently when a simultaneous P wave is incorporated in the QRS. The normal supra-



Fig. 42. Complete atrioventricular heart block during acute myocardial infarction. Ventricular rate 35. Atrial rate 130. Constantly changing relationship between P and R.

ventricular configuration of the QRS complex denotes that the governing impulse arises in a center within the bundle of His or a-v node, below the site of obstruction, and that its subsequent course through the bundle branches and ventricular musculature is normal. If, however, the pacemaker for the ventricles arises in an ectopic focus in the ventricular musculature or in one of the bundle branches, the QRS complexes appear widened, slurred or notched (aberrant QRS). Occasionally complete heart block results from bilateral bundle branch block (p. 306). The electrocardiogram is then characterized by auriculoventricular dissociation with bizarre QRS complexes like those of ventricular premature beats or bundle branch block (p. 306). A distinctive feature in these cases is the tendency for the QRS complex to shift in configuration from the

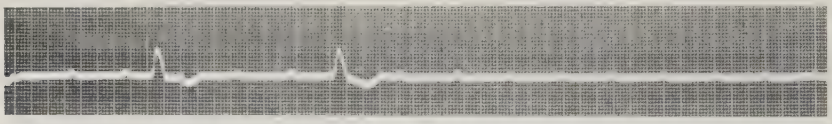


Fig. 43. Complete atrioventricular block with prolonged ventricular asystole.

right to the left, or from the left to the right type of ventricular premature beat or bundle branch block.

Although the P waves in cases of complete heart block are usually normal in configuration, rate and rhythm, they may be absent or replaced by "f" waves when auricular fibrillation is associated. The rate of the P waves may also be accelerated if heart block is combined with auricular flutter or tachycardia.

The P waves may not recur with absolute regularity, for both in partial 2:1 and complete heart block the P-P periods in which a QRS complex falls may be slightly briefer than the other P-P intervals. This indicates that the auricular impulse may in some way be influenced by a preceding ventricular contraction, perhaps through modification of vagal tone.[80] The P waves following a QRS may appear to be premature, but are usually distinguishable from an auricular extrasystole because in the latter the configuration of the P wave is altered as

well as premature. Occasionally this distinction fails because the shape of a P wave in cases of heart block may be abnormal if it occurs early in diastole.[82]

Sometimes there is retrograde conduction from the ventricular pacemaker to the atrium despite the complete heart block. This depends on the time relationship of the idioventricular beat to the preceding normal auricular contraction. In order to produce an auricular response the ventricular impulse must arrive when the auricular musculature is no longer refractory.

Following stimulation of nerve or muscle, there is a period of *complete refractoriness* to further stimulation, followed by a *relatively refractory* period when these tissues respond only to stronger stimuli than are usually effective. Under certain circumstances, during the recovery period following stimulation there is a brief stage when the muscle may respond to weaker stimuli than usual (i. e., subthreshold stimuli). This is known as a *supernormal recovery phase* and is observed occasionally in cases of heart block, early in diastole.[59] Thus, P waves occurring early in diastole may be conducted, while those occurring late in diastole are blocked. The supernormal phase of conduction has also been related to the occurrence of premature beats at this stage of the cardiac cycle.

Etiology and Pathology. The commonest clinical causes of heart block (including all degrees of severity) are:

1. Chronic forms of heart disease, especially severe coronary arteriosclerosis, calcific aortic stenosis (usually rheumatic) and less often other forms of rheumatic heart disease, syphilitic heart disease, syphilitic gumma and gummatous myocarditis, neoplasms and congenital heart disease.
2. Digitalis in full doses and, less commonly, quinidine.
3. Acute infectious diseases, notably rheumatic fever and diphtheria, but at times almost every other infection.
4. The tachycardias. Auricular extrasystoles.

As a rule, the causative factors under the last three headings induce only a functional and transient heart block,[34] while the chronic forms of heart disease, being associated with anatomic lesions, give rise to heart block which is usually but not always permanent. In many instances in which functional disturbances are responsible for precipitating heart block there is also organic heart disease which acts as a predisposing or contributory factor.

I have already stated that various forms of *reflex vagal stimulation* may account for transient heart block, characterized usually by a prolonged auriculoventricular conduction time but occasionally by complete a-v dissociation. Heart block may result from compression of the carotid sinus or pressure over the eyeball through the intermediation of vagal reflexes. Mackenzie[60] had already noted that swallowing, which reflexly stimulates the vagus, produced a failure of ventricular response in a patient who previously exhibited only a prolonged auriculoventricular interval. Similarly Weiss and Ferris[96] described the occurrence of Adams-Stokes attacks with transient complete heart block due to a vagovagal reflex provoked by a traction diverticulum of the esophagus. In at least two of the cases of heart block reported by Holmes and Weill,[31] in which heart block was present when the subjects were in the supine position and abolished by standing, vagal influence was demonstrated.

The heart block caused by *digitalis* may likewise be due to the vagal action of the drug, for it is sometimes abolished by full doses of atropine. However, the heart block is more often caused by a direct inhibitory effect of the

digitalis on the a-v node and bundle.[19] While digitalis may induce heart block of all degrees even in normal subjects,[13] the effect is more readily produced when there is already an underlying conduction disturbance. The a-v block associated with sinoauricular block and a-v rhythm has been mentioned (p. 294); usually these combinations result from digitalis or vagal stimulation or both.

In *rheumatic fever,* prolongation of the P-R interval occurs commonly and is a valuable diagnostic finding; severer grades of heart block also occur. Heart block, often of advanced degree, is an important and serious complication of *diphtheria,* as it denotes a severe diphtheritic myocarditis.[63] Usually these cases end fatally.[88] However, Leys[54] recently reported complete a-v dissociation in a woman of twenty-five years which he believed was caused by an attack of diphtheria at the age of ten. Since heart block is also observed in a vast number of other infections such as pneumonia, scarlet fever,[71] grippe, mumps,[79] German measles,[57] in which lesions of the conduction system have not been demonstrated and are improbable, the heart block may be due in part to a toxic effect on the a-v node and bundle. Such a toxic influence may also contribute to the heart block of rheumatic fever and diphtheria independently of any local lesions. The occurrence of heart block during convalescence from many infectious diseases suggests that vagal influences may be significant.

In most instances of heart block associated with acute infections, there is only a prolongation of the P-R interval. In such cases the P-R interval may often be shortened to normal by the administration of atropine. This suggests a vagal factor in the production of the heart block. Even in cases of prolonged P-R interval due to organic causes such as coronary arteriosclerosis or calcific aortic stenosis, atropine may normalize the P-R interval.

The heart block accompanying many paroxysmal tachycardias such as auricular flutter and fibrillation and occasionally auricular paroxysmal tachycardia is generally believed to result from a functional fatigue and refractoriness of the a-v node and bundle, consequent to the great frequency of auricular impulses trying to gain admission to the ventricles.

Coronary artery disease is the chief cause of permanent heart block, which may be partial or complete. However, transient heart block also occurs following an acute coronary occlusion. Heart block, when present, is almost always the consequence of an occlusion of the right coronary artery since a branch of this vessel supplies the a-v node and bundle in more than 90 per cent of hearts. Massive infarction of the septum is apt to be associated with heart block because an extensive septal infarction usually denotes occlusion of both left and right coronary branches.

That coronary artery occlusion (or severe narrowing) does not more frequently produce auriculoventricular block is explained by two circumstances: (1) Left coronary artery occlusion rarely produces heart block because the conduction tissues almost always receive their blood supply from the right coronary. (2) Right coronary artery occlusion uncommonly produces heart block because the septal branch to the a-v node and bundle comes off very early and the occlusion is usually distal to the origin of this branch. As a rule histologic examination discloses necrosis, degenerative changes or fibrosis of the a-v bundle or of both bundle branches.[112] However, a-v block may result from tissue anoxia due to a deficient blood supply to the a-v node and bundle.[77]

In instances of *calcific aortic stenosis,* which is almost always rheumatic in

etiology, various degrees of heart block may result from extension of the calcific process from the aortic ring to the junctional conduction tissue in the septum. However, conduction disturbances in this disease may be due also to anoxia of the bundle caused by functional coronary insufficiency (p. 608). Calcific aortic stenosis may resemble coronary arteriosclerosis with respect both to conduction disturbance and to the presence of angina pectoris because of relative deficiency of the coronary circulation. Heart block may be due to deposits of calcium in the bundle in association with calcification of the annulus of the mitral valve, with or without concomitant calcification of the aortic valve.[111]

Syphilis is an uncommon cause of organic and usually permanent heart block. The conduction disturbance may be due to a gumma infiltrating the bundle of His or both bundle branches, to a gummatous myocarditis extending from the aorta, or to coronary insufficiency caused by syphilitic aortitis with narrowing of the coronary ostia.

Congenital heart block occurs uncommonly, but is not so rare as was formerly believed.[109, 113, 11] It probably composes 10 to 15 per cent of all cases of complete heart block and one-half of those occurring below the age of fifty.[11, 93, 15] It results from a defect in the course or development of the junctional conduction tissues, and is almost always associated with interventricular septal defects. Congenital heart block without evidence of a septal defect was found in two siblings, in one of whose parents there was also a Wolff-Parkinson-White syndrome.[97] Detailed histologic studies reported by Yater,[109] and Yater, Leaman and Cornell,[113] disclosed a separation of the a-v node from the bundle of His by the central fibrous body. Other rare causes of heart block, usually permanent and associated with anatomic lesions, are bacterial endocarditis with extension of the bacterial inflammatory changes to the septum, neoplasms, tuberculosis and cysts invading the conducting tissues and traumatic lesions. Heart block has also been noted with aneurysm of the sinus of Valsalva,[18] probably of congenital origin.

Age and Sex. In a study of 64 cases of severe heart block, mostly complete, Campbell[11] found that 46 were in the age range between fifty and seventy and that males predominated in the ratio of 4:1.

Clinical Features. Subjective symptoms are generally absent since the rhythm is usually regular and the rate is either normal or slow. Bradycardia is much better tolerated than tachycardia as regards both precordial discomfort and circulatory disturbances. When impaired conduction is limited to prolonged conduction time, there are never any symptoms. In fact, heart block is usually discovered accidentally during routine examinations and first degree heart block (prolonged P-R interval) is a chance discovery in electrocardiographic examinations. On occasion there may be local symptoms consisting of precordial discomfort or palpitation due to relatively long pauses between beats or to the thumping of the strong ventricular contractions following the pause. There may be recurrent sensations "as if the heart stops" accompanied by intense anxiety and other psychogenic symptoms. Weakness, precordial or epigastric pain occurs occasionally.

In most instances of heart block there is no significant circulatory disturbance. Sometimes in the presence of heart block, with slow ventricular rate, the heart may be compensated at rest but not under the stress of exercise. With partial heart block of lesser severity, the heart rate increases with exercise and excitement. On the other hand the degree of block may be enhanced by exercise

and the ventricular rate may be slowed instead of accelerated. When block is complete, the circulation may become insufficient during exercise because of the failure of the ventricle to compensate by an increased rate. An effective circulation is usually maintained even when the ventricular rate is as slow as 20 to 30 per minute. The deficiency in cardiac rate is compensated by the prolonged diastolic period available for ventricular filling and myocardial recovery; this results in an augmented stroke output. But when the pause between beats is sufficiently long (more than 3 to 5 seconds), the patient may experience dizziness or vertigo, faintness or attacks of syncope. These symptoms are observed, as a rule, in the severer grades of partial heart block or in cases of complete heart block, and in older individuals in whom cerebral arteriosclerosis may be a predisposing or contributory factor. A history of syncope or convulsions is not uncommon in the cases of congenital heart block.

The *Morgagni-Adams-Stokes syndrome* (Adams-Stokes; Stokes-Adams) refers to attacks of syncope with or without convulsive seizures due to prolonged asystole (five to ten seconds or more) (Fig. 43). The patient becomes pale, loses consciousness and is found to be pulseless. In more severe attacks (fifteen seconds or more) the pallor is combined with or replaced by cyanosis, the breathing becomes deep and stertorous and a generalized convulsion develops. There may be an associated Cheyne-Stokes respiration.[2, 30] After twenty seconds or longer the twitchings disappear, the pulse returns, normal color is restored and the breathing becomes quiet. Nonfatal paroxysms rarely exceed sixty seconds in duration, but recovery has followed longer periods of asystole lasting five to twenty minutes.[1]

These attacks usually occur when there is a failure of ventricular contraction in the course of complete heart block, or when there is a delay in the establishment of idioventricular rhythm in the transition from normal sinus rhythm to partial or complete heart block.[48] Either nervous influences or progressive coronary insufficiency may explain why the regularly contracting ventricle in complete heart block suddenly stops for more or less prolonged intervals. Similar Adams-Stokes seizures occur when asystole is the result of periods of ventricular tachycardia or fibrillation with or without associated complete heart block[70, 84] (p. 287). Syncope from cardiac standstill may also occur in the normal heart as a result of vagal reflexes from a sensitive or compressed carotid sinus or in instances or sinoauricular block.

Other symptoms and signs observed in cases of heart block are those of the associated causative condition or underlying heart disease. Manifestations of angina pectoris or of congestive heart failure are not uncommon.

Signs of Heart Block. There are no physical signs of prolonged auriculoventricular conduction time. However, when sufficiently prolonged, it may tend to produce a gallop rhythm and the first heart sound may be diminished in intensity. The gallop rhythm results from segregation of the auricular sound by the long P-R interval.

With prolonged auriculoventricular conduction and occasional dropped beats, the heart rhythm is regular while the blocked impulses are denoted by pauses.

With severe degrees of partial heart block, 2:1, 3:1, etc., or with complete heart block, the cardiac rate is slow (40 per minute or less usually, but 50 per minute is common in complete heart block that is congenital, rheumatic or due to digitalis). In cases of diphtheritic heart block there is often a terminal ven-

tricular tachycardia and there may be a high idioventricular rate of 80 to 100.[8] The rhythm may appear regular or, in partial heart block, there may be abrupt transitions in cycle lengths. In complete heart block, the changing time relationship between auricular and ventricular contraction and the consequent change in position of the a-v cusps[17] results in corresponding variations in the intensity of the first heart sound. The auricular sound may be heard faintly between the regular heart sounds, or by coincidence or close proximity with them cause accentuation or reduplication of the first or second sound. In instances of mitral stenosis associated with complete or 2:1 heart block a murmur may be audible with each auricular beat which falls during ventricular diastole.

Not infrequently calcification in the interventricular septum can be demonstrated radiologically in cases of heart block.[103]

Diagnosis. The diagnosis of delayed auriculoventricular conduction can only be made by the electrocardiographic finding of a prolonged P-R interval (or by analysis of jugular venous tracings). Its presence may be suspected from the development of a gallop rhythm[105] or variations in intensity of the first heart sound during or after infectious diseases, especially rheumatic fever.

When the delayed conduction is associated with dropped beats, partial heart block is suspected from the regular rhythm with intermittent pauses. This may have to be distinguished from premature beats in which, however, the pause follows a fast (precocious) beat. Sometimes auscultation fails in this differentiation as the weak sound of the auricular beat may be indistinguishable from the weak sound of a premature beat. Partial heart block is diagnosed essentially by electrocardiographic examination (p. 296).

Severe partial heart block, e. g., 3:2, 2:1 or 3:1 block, or complete heart block should be considered with slow apical and pulse rates of 25 to 50 per minute. Occasionally rates below 15 per minute have been recorded.[16] However, congenital complete heart block is often overlooked because the ventricular rate is relatively fast, 40 to 56,[10] and in diphtheritic heart block it may exceed 80. Congenital heart block has been diagnosed in utero by the fetal electrocardiogram and sound tracings, with simultaneous electrocardiogram of the mother.[35] The diagnosis was suggested by the slow fetal heart rate. Severe partial and complete heart block must be distinguished from each other and from intense sinoauricular bradycardia and from sinoauricular block. Auriculoventricular block may be distinguished from the others by the findings of more auricular ("a") waves in the jugular veins than apical beats. The auricular waves may be observed during the ventricular pauses determined by simultaneous auscultation of the heart. Attempts to increase the heart rate by exercise, atropine or amyl nitrite may be helpful in that the rate increases most in sinus bradycardia and not at all or very slightly in complete heart block. In partial heart block there may be a slight increase in heart rate or an abrupt slowing due to further impairment in a-v conduction. Carotid sinus pressure may further slow the heart rate when the block is partial, or have no effect in the presence of complete heart block. Complete heart block may also be distinguishable from partial heart block by the irregular change in intensity of the first heart sound in the former. From time to time there is a sharp accentuation of the first sound at the apex ("cannon sounds").

The diagnosis of severe heart block may be suspected from the occurrence of Adams-Stokes seizures. Usually a-v block is discoverable in electrocardiograms taken between attacks, but rarely heart block occurs only during the

attack. Among the diagnostic features confirming the suspicion that the attack is due to heart block are: absence of heart or pulse beat during the attack while the auricular sounds may be heard on auscultation and the auricular "a" waves may be seen in the cervical veins; the relatively longer duration of the attack in heart block than in vagal cardiac standstill. The finding of a very slow pulse after recovery also suggests that the syncope was due to heart block. However, the heart rate may be 90 or higher as the patient is recovering, especially if he is under the influence of drugs; after several hours the pulse slows again. For electrocardiographic diagnosis of complete heart block, see p. 297.

Prognosis. The clinical significance and the prognosis of heart block depend on the causative factor. Heart block due to vagal reflexes, to digitalis toxicity or to extreme tachycardia is usually insignificant in itself and transient in duration. The underlying conditions responsible for the vagal reflex, the tachycardia or for the administration of digitalis may, however, be serious. They, not the heart block, determine the prognosis.

Similarly, various grades of heart block occurring with infectious diseases are usually self-limited in duration (hours, days or a few weeks) and scarcely modify the outlook of the basic disease itself. However, the heart block occurring with rheumatic fever, and less often with other infections, may persist, although this is exceptional. In diphtheria, heart block is often of ominous significance but only because it occurs in intensely toxic cases in which there is a severe myocarditis. However, if recovery ensues, there is no evidence of chronic diphtheritic heart disease. In general it may be stated that the seriousness attached to heart block is justified only when it is a manifestation of a serious underlying disease or toxic state. Sometimes the observation of heart block first suggests the search for and the discovery of some underlying disease or digitalis intoxication.

Heart block is often associated with heart disease, and in such cases the outlook varies according to the type of heart disease and its severity. Congenital heart block in subjects surviving childhood is usually compatible with normal activities (including pregnancy, childbirth and manual work) and with a normal life span.[11] Heart block may be transient during an attack of acute coronary occlusion, but often it persists and becomes progressively more complete. Heart block in syphilitic heart disease may diminish following antisyphilitic therapy, possibly due to resorption of a gumma.

The development of the Adams-Stokes syndrome with heart block is often of serious omen. Cases of heart block associated with bundle branch block are said to be associated more frequently with Adams-Stokes syndrome and an unfavorable prognosis than those associated with the normal supraventricular type of QRS complex.[37] An attack may occur at the onset of heart block but may never again appear. On the other hand these attacks may appear infrequently at first, but shortly occur more and more often and with increasing severity. They often denote severe myocardial disease. Death may occur during one of the attacks due to prolonged ventricular standstill. As a rule death occurs suddenly in patients with heart block and Adams-Stokes syndrome. In other cases of complete heart block associated with coronary and hypertensive heart disease, but without Adams-Stokes attacks, heart failure is the common cause of death.

Treatment. Treatment is rarely indicated for the heart block itself, as it usually is not responsible for symptoms and clears spontaneously. Treatment of

the causative factor may result in abolition of the heart block. Digitalis, quinidine and opiates should be stopped. If these are responsible for the heart block, it will disappear rapidly. If their use is essential, the heart block may not recur with smaller doses.

Heart block may require more specific treatment when it is itself responsible for symptoms, especially dizziness, faintness or Adams-Stokes seizures. Treatment may be necessary for the acute attack or to prevent recurrent attacks. For the former epinephrine hydrochloride is the drug of choice, 0.3 to 1 cc. (5 to 15 minims) being injected subcutaneously or intramuscularly. When the attacks recur with great frequency, e. g., during an acute attack of myocardial infarction, this dose may have to be repeated every two hours for a day or two. After the first injection or two, epinephrine in oil (1 cc. contains 2 mg. of epinephrine) may be given intramuscularly for prolonged effect. This may be repeated after twelve to twenty-four hours if necessary. The intervals can be prolonged and the drug finally discontinued if the attacks regress or subside. With dangerously prolonged ventricular standstill, an intracardiac injection of epinephrine may be lifesaving. It is important to obtain electrocardiographic tracings to be certain that asystole is due to ventricular standstill and not to ventricular tachycardia-fibrillation. Epinephrine is useful in the former condition because it increases ventricular irritability. On the other hand, because of this action it is contraindicated in ventricular fibrillation which it tends to prolong rather than alleviate.

Atropine sulfate, 1 to 2 mg. (1/60 to 1/30 grain), may be administered when heart block is due to vagal influences. It is sometimes given in conjunction with epinephrine in attacks of Adams-Stokes syndrome.

For more chronic use, or to alleviate attacks of moderate frequency in ambulant persons, other sympathomimetic drugs may be given orally: ephedrine, 15 to 30 mg. (¼ to ½ grain) three to five times daily; paredrine, 20 to 60 mg. (⅓ to 1 grain) three to five times daily.[65] If palpitation or nervous symptoms develop, these drugs should be combined with sedatives. Atropine may be combined with ephedrine, paredrine, etc. Homatropine methylbromide (novatrin), 10 grains, has been substituted for atropine because of the latter's unpleasant drying effect on the mouth. The novatrin may be given in doses of 6 mg. (1/10 grain) to the point of tolerance.

Barium chloride has been used in doses of 20 to 60 mg. (⅓ to 1 grain) because of its tendency to increase ventricular irritability, but its efficiency is questionable.

Digitalis would seem to be contraindicated because of its vagal stimulating effect and its tendency to impair a-v conduction by direct action on the a-v node and bundle. Nevertheless, it has on occasion prevented attacks, relieved symptoms due to heart block or eliminated the heart block itself when all other measures failed. The explanation for this effect of digitalis is uncertain but it may be related to its improvement of myocardial efficiency. Of course, when there are definite signs of congestive heart failure, digitalis should be administered as usual, regardless of the heart block.

Thyroid extract and thyroxin have been recommended both for acute attacks of ventricular asystole and to prevent recurring attacks. Its value for this purpose is unproven. When the episodes of asystole are proven to be due to ventricular fibrillation, quinidine is the drug of choice (p. 287); when due to ventricular standstill, quinidine is contraindicated.

BUNDLE BRANCH BLOCK

Bundle branch block refers to a delay in or obstruction to the conduction of impulses in one of the branches of the bundle of His. The obstruction may be complete or incomplete. The terms intraventricular conduction defect or intraventricular block have been applied to electrocardiographic patterns believed to represent incomplete bundle branch block or multiple obstructions in the Purkinje fibers. The term arborization block,[69] formerly employed to denote extensive block in the arborization fibers of Purkinje, has generally fallen into disuse. Pathologic studies have thus far failed to disclose such distinct correlations between the anatomic findings and the electrocardiographic patterns. The differentiation into complete bundle branch block, incomplete bundle branch block and intraventricular block is essentially electrocardiographic.

Chiefly on the basis of electrocardiographic findings, a sharp division has been made into right and left bundle branch block. Left bundle branch block has been reported to occur four to six times as often as right bundle branch block,[41] but more recent studies suggest that the stated predominance of left bundle branch block has been exaggerated.[5] The higher incidence of left bundle branch block is related to the greater frequency of damage to the left ventricle. Occasionally a complete block of both branches produces a condition identical with auriculoventricular block.[112]

The normal sinus impulse, after traversing the a-v node and bundle, courses simultaneously through both bundle branches and their smaller ramifications. In this way the excitation process reaches both ventricular cavities, passes from the endocardial to the epicardial layer and activates both ventricles at the same time. The QRS complex of the electrocardiogram represents the summation of the excitation process in both ventricles; its normal duration is 0.06 to 0.09 second.

If there is an obstruction in one of the main bundle branches, e. g., the left, the excitation process must travel along the (functionally) intact right branch; the left ventricle is activated indirectly by passage of the impulse from the right bundle branch through the interventricular septum to the arborization branches in the left ventricle. The excitatory process travels much more rapidly through the specialized tissues of the conduction system than through the cardiac musculature. Therefore about 0.04 to 0.05 second is lost in passage of the impulse to the left ventricle through the septal muscle instead of along the left bundle branch. This delay in reaching the left ventricle is disclosed electrocardiographically by prolongation of the QRS complex, while the abnormal route taken by the excitatory process is documented by an abnormal configuration of the QRS (aberrant QRS). Bundle branch block was produced experimentally and its electrocardiographic pattern described by Eppinger and Rothberger.[21]

Bundle branch block may also be disclosed by asynchronism of ventricular contraction as seen by fluoroscopy or kymography or by simultaneous phonocardiograms and tracings of the carotid and jugular venous pulses.[4] In left bundle branch block there is a relative delay in the carotid pulse, in right bundle branch block a relative delay in the v wave of the jugular venous pulse tracing.

The Electrocardiogram. The essential features of bundle branch block are the *prolonged QRS interval* (0.12 second or more) and the *slurring and notch-*

ing of the QRS complex. The appearance of the QRS resembles that of a ventricular premature beat.

The P wave and the P-R intervals are usually normal since the pathway of the sinus impulse is normal until it reaches the block in the bundle branch. However, it is not uncommon for bundle branch block to be associated with auriculoventricular heart block and therefore with a prolonged P-R interval.[89] Occasionally an intraventricular conduction defect (with wide and notched QRS complexes) accompanies auricular fibrillation. Under these circumstances P waves are absent but fibrillation "f" waves may be visible while the QRS complexes occur at irregular intervals. With very rapid ventricular rates bundle branch block may be indistinguishable from ventricular tachycardia. The diagnosis of bundle branch block must always be made with reserve during any paroxysmal tachycardia in which the P waves and P-R intervals are obscured.

Localization of Left and Right Bundle Branch Block. Since the earliest experimental studies of bundle branch block in dogs, the common bundle branch block pattern has been attributed to right bundle branch block and the uncommon form to left bundle branch block.[52] A host of observations have provided convincing and now generally accepted evidence that this nomenclature should be reversed. The confusion probably arose from the differences between the dog and human with regard to the relationship of the cardiac chambers to each other, to the chest wall and to the axis of the body. The position of the dog's heart is essentially vertical while that of the human is more horizontal or oblique.

Fahr[24] and also Mann,[61] on theoretical grounds, and Oppenheimer and Pardee,[68] on the basis of pathologic studies, first indicated that the accepted patterns for right and left bundle branch block should be reversed. Then Barker, Macleod and Alexander,[3] by electrical stimulation of the right ventricle of the human heart, exposed for drainage of a purulent pericarditis, demonstrated that the main deflection of the QRS complex was upward in extrasystoles from that chamber. Since, in a block of the left bundle branch, the excitation process must pass from the right ventricle to the left, the electrocardiographic pattern of left bundle branch block in any lead resembles that of a right ventricular extrasystole, and of right bundle branch block that of a left ventricular extrasystole. According to the above observations, the common electrocardiographic form of bundle branch block, formerly termed right bundle branch block, is really due to a block of the left main bundle branch and is characterized by a major upward deflection in lead I.

This conclusion was confirmed by similar stimulation experiments of the human heart by Marvin and Oughterson[62] and Lundy and Bacon.[58] Furthermore, Kountz and his associates[44] sectioned the left bundle branch of human hearts which were revived after death by perfusion of the heart and lungs in situ. They found that the electrocardiographic pattern was characterized by an upward major deflection of the QRS in lead I and by other features seen in the commoner type of bundle branch block. Similar findings were noted after experimental bundle branch block in monkeys.[90] Finally, precordial leads yielded important supporting evidence of the correctness of the new terminology as well as practical assistance in the electrocardiographic diagnosis and localization of less typical forms of bundle branch block.

It is known that the peak of the R wave as found in precordial leads denotes the time of arrival of the excitation wave at the site beneath the precordial electrode. By taking simultaneous records of lead I and a precordial lead from the right side (CF_1CF_2) or from the left side of the heart (CF_6), Wilson, Macleod and Barker[102] were able to discover any delay in conduction by noting when the peak in the R wave occurred in lead I and the precordial lead. They found that in electrocardiograms now interpreted as indicating left bundle branch block the peak of the R wave was not delayed in the precordial lead taken from the sternal region (right side of heart) but was delayed in the lead taken from the apex or to its left. That is, the stimulus arrives earlier over the right ventricle when there is a block of the left bundle branch. The converse was discovered in right bundle branch block. These findings were in harmony with the newer interpretation of left and right bundle branch block patterns.

Furthermore, by this method or by the use of unipolar precordial leads it also became possible, in doubtful instances, to determine the presence or absence as well as the location of the bundle branch block.[101] Since activation of the myocardium underlying a precordial lead is denoted by a negative (intrinsic) deflection, this negative (S, or QS) wave will be delayed if the electrode is placed on the side of the block. In left bundle branch block the descending limb of a broad R (i.e., the intrinsic negative) deflection is delayed in leads V_5 or V_6 while the negative deflection Q or QS occurs early in leads V_1 or V_2 over the right side of the precordium.

Left Bundle Branch Block. The *typical pattern* in standard leads is characacterized by (Figs. 44–45):

1. QRS intervals of 0.12 second or more.
2. Conspicuous notching or slurring of the QRS complexes.
3. QRS complexes of discordant type with the major initial deflection (R) upward in lead I and the major initial deflection downward in lead III. There is

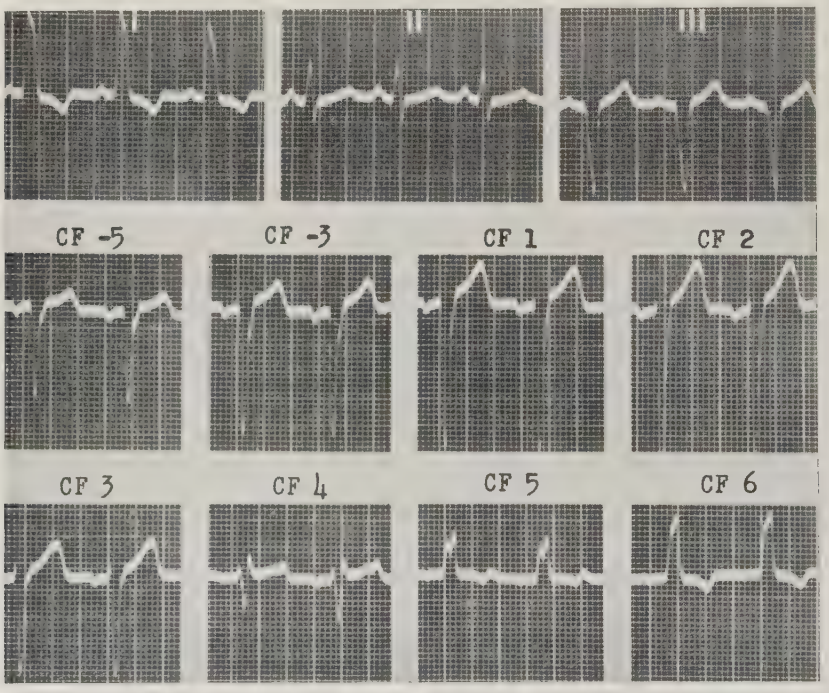


Fig. 44. Left bundle branch block. QRS in standard leads = 0.12 second. Early intrinsic deflection in CF_1 and CF_2. Delayed intrinsic deflection in CF_5 and CF_6.

no conspicuous S wave in lead I. A Q wave seldom occurs in lead I.[86] When it does, it may be due to previous septal infarction or to a change of position of the heart during respiration.[47]

4. Large T waves which are opposite in direction to the major ventricular deflections, i. e., T is inverted in lead I and upright in lead III. The S-T interval is usually elevated or depressed in the same direction as the peak of the major initial deflection.

However, the electrocardiographic pattern of left bundle branch block may vary from this typical pattern, but only as regards items (3) and (4) above. Such variations are termed atypical bundle branch block. The fact that we are dealing with left and not right bundle branch block is determined

from inspection of lead I and more definitely from precordial leads. Thus as a rule widening (0.12 plus second) and notching of the QRS complex with the major initial ventricular deflection upward in lead I denotes left bundle branch block (unless there is a broad S wave). The major initial deflection may also be upward in lead III (concordant curves) and the T waves may be deflected in the same instead of in the opposite direction to the main initial deflection, in either lead I or III. The reasons for these variations from the typical pattern and even for resemblances to the pattern of right bundle branch block are the presence of enlargement of one or both of the chambers of the heart, the location and extent of associated myocardial damage and especially the posi-

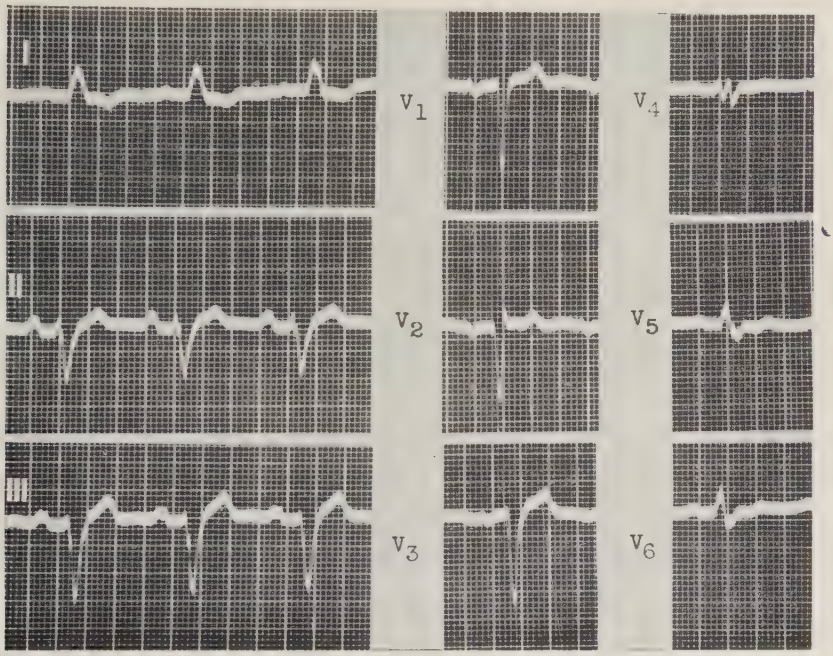


Fig. 45. Left bundle branch block. Early intrinsic deflection in V_1, V_2 and V_3 over right side of precordium. Notching, widening and late onset of downstroke of R (intrinsic deflection) over left side of precordium.

tion of the heart in the chest. Discordant curves usually occur with normal or transversely placed hearts and concordant curves with vertically placed hearts. In vertically placed hearts the pattern in the standard leads may tend to cause a left bundle branch block to resemble a right bundle branch block, and a horizontally placed heart may cause right bundle branch block to simulate a block of the left branch.[101]

Precordial leads in patients with *left bundle branch block* (Figs. 44, 45), when applied near the sternum (CF_1CF_2) show a very small R wave (intrinsic deflection) or none at all, a large S wave, and usually a large T wave. The R wave occurs early, i. e., 0.02 to 0.05 second after the onset of the QRS complex, or there is an early onset of an S or QS wave. When taken from the left side of the heart, at the apex or beyond (CF_5CF_6), an R wave is not only slurred and notched but appears late; i. e., the peak of the R wave does not appear until 0.08 to 0.10 second after the beginning of the QRS in that

lead. (Normally the interval is 0.02 to 0.05 second.) The R wave is usually not well developed in left bundle branch block until the precordial lead is applied outside the apex (CF_6).

Right Bundle Branch Block. Typical right bundle branch block is characterized electrocardiographically in the standard leads by (Fig. 46):

1. QRS complexes 0.12 second or more in duration.
2. QRS complexes which are conspicuously notched or slurred.
3. QRS complexes which are discordant, and in which the main initial deflection (S) is downward in lead I and the main initial deflection (R) is upward in lead III.

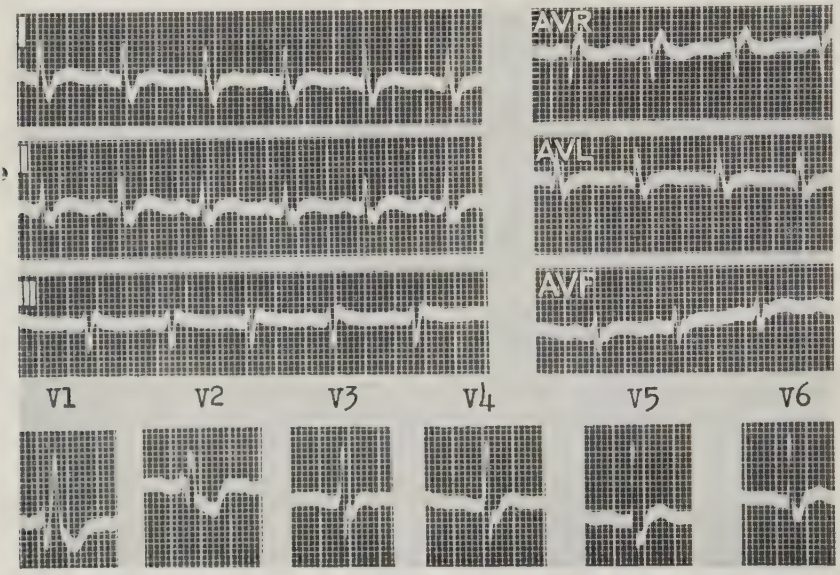


Fig. 46. Right bundle branch block. S_1 type. Intrinsic deflection (downstroke of R) delayed in V_1 and V_2, early in V_5 and V_6.

4. Large T waves opposite in direction to the main initial ventricular deflection, i. e., T is upright in lead I and downward in lead III.

Many variations from this pattern have been observed and classified as *atypical right bundle branch block*. It is questionable whether these variations denote a significant difference in the character of the block of the right bundle branch. They probably represent modifications caused by associated asymmetrical ventricular enlargement, myocardial lesions and differences in the position of the heart. According to the studies of Bayley[5] and of Wilson and his associates,[102] there are four or five types of right bundle branch block pattern, of which the first is the typical one described above. The chief variations (aside from the essential criteria of wide [0.12 second or more] notched and slurred QRS complexes) include: (a) There is a broad S wave in lead I, which however is not as tall as R. (b) There is a broad S_1 and positive T_1, but the prominent deflection in lead III is a deep Q followed by a prominent but smaller R. (c) R_1 is tall and S_1 is small but broad, while S_3 is broad and deep and T_1 and T_3 are variable in direction. (d) R and S are small in lead I, but S_3 is deep and broad and T_3 is upright.

An analysis of these variations discloses that in right bundle branch block there is always a broad S wave in lead I, i. e., the deflection of longest duration (but not necessarily of greatest amplitude) is directed downward. When S_1 is not very prominent, S_2 and S_3 are. In general also the QRS complex is definitely diphasic or triphasic in leads with prominent deflections, while this complex is essentially monophasic in cases of left bundle branch block.

The *precordial leads in right bundle branch block* are of special importance because of variable patterns in the standard leads and because of the great influence of changes in the position of the heart. The characteristic findings are (Fig. 46):

1. R waves (pre-intrinsic deflection) which are prominent in leads V_1, V_2 (right side of heart), and which occur late. The peak of the R wave occurs 0.08 to 0.10 second or more after the beginning of the QRS instead of the normal of 0.02 to 0.05 second. The R wave is broad and notched and often bifid, in which circumstance it has been found that the second peak corresponds to the R wave peak in other precordial leads. A prominent Q in these leads suggests septal infarction.

2. Slender R waves which are prominent in leads from the left side of the heart (CF_5CF_6) but which occur early. The peak of R_5 or R_6 occurs 0.02 to 0.05 second after the beginning of the QRS complex. The R wave is usually followed by a broad, shallow S.

Incomplete Bundle Branch Block. Intraventricular Conduction Defects. These terms have been applied to electrocardiographic patterns resembling bundle branch block, in which:

1. The QRS interval is 0.10 to 0.11 second. This is believed to denote some delay in, or incomplete obstruction to, conduction through the main bundle branches or their ramifications.

2. The QRS complexes are often notched or slurred. When present, this suggests a deviation from the normal pathway of excitation of one or both of the ventricles.

When the above pattern resembles that of left bundle branch block, i. e., the main deflection is upward in lead I, downward in lead III with T waves in opposite direction, but the QRS interval measures only 0.10 to 0.11 second, it may be termed incomplete left bundle branch block. When it resembles the typical right bundle branch block except for the duration of the QRS wave, it may be termed incomplete right bundle branch block. Intraventricular conduction defect or block refers to a widening, notching and slurring of the QRS complex without conformation to one of the above distinct patterns. Often in the latter group the QRS complexes are of low voltage. It is possible that this represents a conduction defect with extensive myocardial damage.

In some electrocardiograms of patients with marked left ventricular enlargement the pattern is that of left axis deviation (p. 37) and the QRS interval measures 0.10 to 0.11 second. This combination may be indistinguishable from incomplete left bundle branch block. The prolonged QRS interval may represent the longer period required to activate the enlarged left ventricle. However, precordial leads will not disclose the delay in appearance of the peak of the R wave when the leads are applied over the left side of the heart CF_5CF_6. A similar resemblance of curves of right ventricular preponderance to those of incomplete right bundle branch block is observed much more rarely.

Recurrent (Paroxysmal) and Intermittent Bundle Branch Block. When bundle branch block appears temporarily but continuously for hours or days, we speak of it as paroxysmal bundle branch block. Recurrent attacks of bundle branch block have been described repeatedly.[99] Such recurrent attacks may be "functional" in cases of tachycardia without underlying cardiac disease, or they may occur in cases of organic heart disease.

Occasionally QRS complexes denoting bundle branch block alternate with normal QRS complexes; or they may appear more or less regularly in ratios of 1:1, 1:2, or 3:2 block, etc., the first figure representing the number of normal complexes and the second, the corresponding number of block complexes. Such curves are termed intermittent bundle branch block. They probably result from partial block or defective bundle branch conduction of variable degree. Sometimes there is a progressive change from normal to typical QRS complexes of the branch block variety, resembling the Wenckebach phenomenon of partial auriculoventricular block with dropped beats. Presumably the conduction time through the bundle branch increases gradually until there is a block. This permits recovery of the bundle branch and the next impulse passes normally and so on, seriatim.

Etiology and Pathology. The great majority of cases of bundle branch block is due to coronary arteriosclerosis, usually with recent or old occlusion and associated hypertension. The bundle branches may be damaged or blocked by infarction of tissue. Or a more gradual, degenerative and fibrotic alteration may be due to chronic coronary ischemia. Pathologic and electrocardiographic correlations are often uncertain due to the paucity of studies and especially to technical difficulties. Furthermore, lesions are commonly found involving both branches;[110] the electrocardiogram may then document the asynchronism in conduction in the two branches. The bundle branches, like the a-v node and bundle of His, are often supplied by the right coronary artery and by a vessel which leaves the main right coronary very early (p. 321). Therefore, the bundle branches may not be affected by occlusions of the left coronary artery or of the right coronary artery distal to the origin of the septal branch supplying the conduction system. When rheumatic heart disease with mitral stenosis is associated with bundle branch block, the pattern is usually that of right bundle branch block.[94, 5]

Other causes of bundle branch block are similar to those responsible for auriculoventricular block: calcific aortic stenosis, other forms of rheumatic heart disease, syphilitic gumma or luetic aortitis with gummatous myocarditis, and even more rarely diphtheria, tumors, cysts, trauma and bacterial endocarditis. Quinidine and digitalis may cause a toxic impairment in bundle branch conduction. A toxic bundle branch block may occur in uremia. Functional disturbance may result from any severe paroxysmal tachycardia and auricular flutter, with subsidence as the rate slows,[20] and from acute right ventricular strain due to massive pulmonary embolism. According to Rasmussen and Moe,[73] left bundle branch block is due most often to conspicuous dilatation and hypertrophy of the left ventricle, rather than to organic lesions in the conduction system. But this viewpoint does not appear to be supported by clinical and pathologic observations.

The *age and sex* of patients with bundle branch block is determined by the cause. Since coronary arteriosclerosis is the chief cause, bundle branch block is observed mostly among males beyond the age of fifty.[98, 75]

Clinical Features and Diagnosis. There are no symptoms of bundle branch block as such. But there may be symptoms of the causative disease. Likewise there are usually no specific diagnostic signs. Occasionally bundle branch block is associated with paroxysmal or persistent heart block and syncopal attacks of the Adams-Stokes type.[55, 89] A palpable, reduplicated apical impulse[40, 42] and reduplication of the first or both sounds, due to slightly asynchronous contraction of the ventricles,[104] may suggest the presence of bundle branch block, but as a rule the diagnosis is not made on physical examination.[29, 51] Bundle branch block is not infrequently associated with a diastolic gallop rhythm and occasionally with pulsus alternans. The latter two findings should suggest the possibility that bundle branch block is also present, especially if the heart rate is less than 90 per minute.

The definite diagnosis of bundle branch block, however, depends on electrocardiographic study (p. 306) and for accurate localization curves taken with precordial leads are necessary.

Course and Prognosis. Bundle branch block occurs transiently or may persist permanently. When due to toxic factors which may be removed, bundle branch block is a temporary reversible condition. Intraventricular block associated with the paroxysmal tachycardia of auricular flutter subsides when the paroxysm ceases. The bundle branch block associated with severe coronary arteriosclerosis and other forms of organic heart disease is usually persistent, but I have several times seen bundle branch block develop at the onset of an acute coronary occlusion and disappear within a few days. Bundle branch block may recur intermittently for a period of months and then disappear or become permanent.[45, 99] Kalett[36] reported a case of bundle branch block with spontaneous remission after four years. But as a rule, when the branch block persists without remission for several months, it is likely to be permanent.

Too much importance has been attached to the prognostic significance of bundle branch block. It has been stated that the survival period averaged one to two years, although more recently it has been recognized that some patients with this condition survived five to fifteen years or longer.[6, 72] Actually the prognosis depends on the underlying cause. The unfavorable prognosis usually applied to bundle branch block corresponds to the prognosis of coronary occlusion, which is the commonest cause. As in recent years we have become aware that the prognosis of coronary occlusion is more optimistic than was formerly thought, there has been a correspondingly more favorable outlook for bundle branch block. Furthermore, bundle branch block occurs more frequently in the younger age groups than was formerly believed; in these there is no apparent evidence of heart disease and the outlook is benign.[46]

Right bundle branch block is considered to offer a more favorable prognosis than left bundle branch block.[72] Such generalization must be accepted with reserve, especially in view of the uncertainties as to the interpretation of patterns now believed to represent right bundle branch block. In general, it is safer to evaluate the patient and his disease as a whole, rather than to base a prognosis on the presence and type of bundle branch block.

Treatment. Treatment is directed toward any underlying or associated condition. The presence of bundle branch block in itself is no indication for treatment. However, when it results from digitalis or quinidine or other intoxication, the causative agent should be eliminated if possible.

SHORT P-R INTERVAL WITH WIDE QRS (WOLFF-PARKINSON-WHITE SYNDROME)

Electrocardiograms resembling those of bundle branch block but with a short P–R interval have been repeatedly noted in young and apparently healthy individuals who are subject to attacks of paroxysmal tachycardia. Isolated cases were documented by Wilson[100] and others,[28] but interest became widespread only after Wolff, Parkinson and White[107] in 1930 reported 11 cases and defined the condition as a distinct entity. For this reason it is often termed the Wolff-Parkinson-White (W-P-W) syndrome. In 1940 Hunter et al.[33] collected 90 cases from the literature and added 19 of their own.

The essential diagnostic feature is a *distinctive electrocardiogram* (Fig. 47) in which (1) the P–R interval is abbreviated, measuring 0.10 second or less,

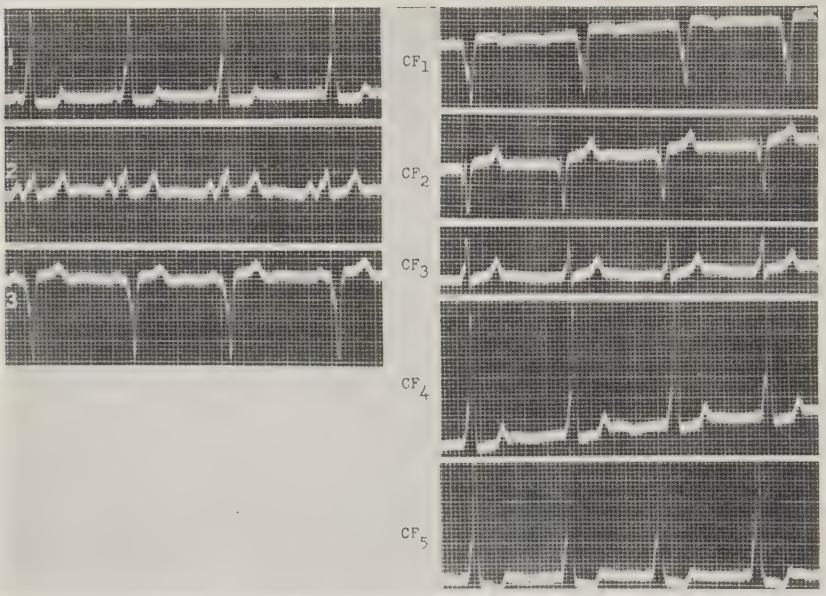


Fig. 47. Wolff-Parkinson-White syndrome. Short P-R interval with bundle branch type of QRS (0.13 second in lead I).

and (2) the QRS complexes are widened (0.11 to 0.14 second) and slurred, with T waves often in the opposite direction to the main deflection of the QRS. The shortening of the P–R interval is exactly compensated by the widening of the QRS complex. Consequently the interval from the onset of the P wave to the end of the QRS remains normal.

The essential clinical feature is the tendency to recurrent attacks of paroxysmal auricular tachycardia. Occasionally auricular fibrillation and rarely ventricular tachycardia[50] have been observed.

The syndrome occurs at all ages, but chiefly below the age of thirty and more commonly in males. Aside from the tendency to experience paroxysmal tachycardia, these subjects are apparently healthy. But recently there have been reports of associated organic heart disease in some cases.[33, 56] And even in the absence of organic heart disease the condition is not always benign, for deaths have occurred suddenly in the course of an attack of paroxysmal tachycardia.[39]

The distinctive electrocardiographic features may disappear spontaneously or when the heart rate is increased by exercise or atropine. In the case reported by Wilson,[100] that of a man aged twenty-three years, the electrocardiographic abnormalities appeared after stimulating the vagus nerve or spontaneously. When they appeared spontaneously, they could be abolished by the administration of atropine. Subsequent reports have been conflicting as to the regularity with which the electrocardiographic changes can be eliminated by atropine and exercise. Quinidine[76] and large doses of digitalis[83] have been observed to restore a normal electrocardiogram in some cases, but in another case digitalis widened the QRS complex.[25] When these persons experience a paroxysm of tachycardia, the widened ventricular complexes assume a normal configuration (except in one case reported by Movitt[64]). During paroxysms of auricular fibrillation the QRS complexes appear aberrant and may be wider than during periods with sinus rhythm,[67] but the absence of P waves during auricular fibrillation prevents a differentiation of wide QRS complexes of the W-P-W syndrome from those due to true bundle branch block or ventricular extrasystoles. The QRS of the W-P-W syndrome may conceal the Q waves associated with posterior cardiac infarction.[43a]

Mechanism. The mechanism responsible for the W-P-W syndrome is uncertain, although several theories have been offered.[33, 66] Wolff, Parkinson and White[107] attributed the electrocardiographic changes to excessive vagal tone because they could abolish them with atropine or exercise, and because occasionally the electrocardiographic abnormalities could be induced by vagal stimulation. This theory was rejected because these effects of atropine or vagal stimulation could not be confirmed in many other cases, and because the electrocardiographic changes could not be harmonized with the known effects of vagal stimulation.

The most generally accepted theory is that of Holzmann and Scherf[32] and of Wolferth and Wood,[106] who postulated the existence of an anomalous aberrant pathway between the atria and ventricles by which the sinus impulse activated the latter chambers. Wolferth and Wood[106] suggested that this aberrant pathway might be similar to the so-called bundle of Kent, a structure in the heart of the rat, bridging the auriculoventricular groove.[38] Subsequently this hypothesis received support by the postmortem discovery of such an accessory bundle in the heart of a child who had exhibited this syndrome during life, and who died during an attack of paroxysmal tachycardia.[108] (See also Oehnell.)[66] Histologic demonstration of an accessory right lateral conduction bundle was reported also in a case of septal infarction with complete heart block and intermittent anomalous a–v excitation (W-P-W syndrome[49]). The theory of an accessory pathway was also supported by the experimental production[9] of a short P–R with wide QRS when the normal conduction system was short-circuited by a vacuum tube amplifier, analogous to the alleged short-circuiting effect of an accessory conduction bundle. By reversing the connections so that amplified ventricular currents stimulated the atria, paroxysms of tachycardia were induced. Although it is usually believed that the aberrant short conduction pathway connects the right atrium and right ventricle, there are cases of W-P-W syndrome in which the left ventricle is activated before the right.[74, 87]

According to the theory of Wolferth and Wood,[106] the short P–R interval is due to the shorter, more direct pathway through the accessory bundle from the

atrium to the ventricle, while the prolongation of the QRS results from premature activation of one ventricle. The altered configuration of the QRS, especially in its early portion, is attributed to the abnormal course of the impulse when it first reaches the ventricle. The anomalous pathway is said to predispose to attacks of paroxysmal tachycardia by facilitating retrograde conduction of the impulse (reentry) into the atrium, where under favorable circumstances the abnormal rhythm is initiated. While this theory appears to be the most satisfactory now available, there are a number of criticisms which have led to other explanations.[26]

In a study of records taken with precordial leads, Boyer[7] found that the electrocardiographic changes in the Wolff-Parkinson-White syndrome did not accord with those expected in cases of bundle branch block (p. 306). Similar observations with precordial leads by Rosenbaum et al.[78] support the view that in the W-P-W syndrome auricular impulses reach the ventricles not only by way of the a-v node and bundle, but also by one or more additional channels.

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PART III

THE CORONARY CIRCULATION AND DISTURBANCES IN CARDIAC BLOOD SUPPLY

14

THE CORONARY CIRCULATION

The Blood Supply to the Heart. The blood supply to the heart[33, 59, 11] is provided by the left and right coronary arteries, the first branches of the aorta, which arise in the left and right aortic sinuses, respectively. The left coronary artery divides into two major branches, the left circumflex and the left anterior descending, which are equal to the right coronary artery in size and importance. The left ventricle is supplied by the left coronary artery, except for the upper (basal) half of the posterior surface which is supplied by the right coronary artery. The right ventricle receives most of its blood supply from the right coronary artery, but the medial portion of the anterior surface and the lower third of the posterior surface near the anterior longitudinal sulcus are supplied by branches of the left coronary. The sinoauricular node is supplied by the right coronary artery in 60 to 75 per cent of hearts and by the left coronary in the remainder. The atrioventricular node is supplied by a special vessel, the ramus septi fibrosi, which arises from the right coronary artery in 90 per cent of hearts. The bundle branches receive their blood supply from both the left and right coronary vessels. The blood supply to the different muscle bundles has been described by Robb and Robb.[54]

Ordinarily the left circumflex artery supplies the anterolateral surface, the obtuse (lateral) margin and most of the posterior surface of the left ventricle. In about 10 per cent of hearts, this artery is larger than usual and may supply all of the posterior surface of the left ventricle and part of the posterior surface of the right ventricle, areas usually supplied by the posterior descending branch of the right coronary artery. In another 10 per cent, the left circumflex artery is smaller than usual and supplies little or none of the posterior surface of either ventricle. According to these variations in the size of the left circumflex artery, the coronary circulation has been classified as balanced, or with a left or right coronary preponderance.[5] Blumgart, Schlesinger and Davis[5] found that infarction occurred most frequently and the mortality after acute infarction was highest after an arterial occlusion in the hearts with left coronary artery preponderance.

Myocardial Capillaries. Ultimately the capillaries and their contents represent the determining factor in the nutrition of the heart muscle. When growth of the heart is completed, there is approximately one capillary for each muscle fiber[58] and there are between 3000 and 4000 capillaries per square millimeter of muscle. In hypertrophied hearts the capillary-fiber ratio remains 1:1, but the

concentration of capillaries per unit area of muscle tissue is greatly reduced, since the individual fibers are enlarged.[55] This renders the hypertrophied heart more susceptible to myocardial ischemia and to heart failure (p. 51).

The Cardiac Venous Return. The venous return from the heart is effected through (1) the coronary sinus, which drains most of the blood which had been supplied by the left coronary, and empties into the right atrium; (2) the anterior cardiac veins which drain most of the blood supplied by the right coronary artery[31] and empty directly into the right atrium and (3) the thebesian veins,[64, 43] which open directly by small foramina into the cavities of the heart, but chiefly into the right ventricle.[40] According to the experiments of Evans and Starling,[16] and of Anrep and associates[1] on heart-lung preparations, the coronary sinus outflow represents 60 to 70 per cent of the total coronary inflow but this percentage may be very variable under different experimental conditions.[39, 37] Recent studies indicate that the left ventricle is drained chiefly by the coronary sinus, the right ventricle by the anterior cardiac veins and that under ordinary conditions the flow through the thebesian veins is small or insignificant.[31]

In addition to the thebesian veins other luminal vessels connect coronary arteries or arterioles directly with the cardiac chambers.[65] These include (a) the arterioluminal vessels, which are of arteriolar size, and (b) the arteriosinusoidal vessels, which are of capillary size with wide irregular lumens. Glass beads injected into the coronary arteries were regularly recovered from each ventricular cavity, the beads ranging from 100 to 400 micra in diameter.[51] Glass spheres, from 70 to 170 micra in diameter, were also recovered from the coronary sinus, denoting the presence of arteriovenous channels of larger size than capillaries.

Coronary Anastomoses and Collateral Circulation. Three types of coronary vascular anastomoses have been noted: (1) *Intercoronary anastomoses* between branches of the same or different major coronary arterial rami.[33, 60] (2) Extrinsic coronary anastomoses between the coronary arteries and the vessels of the epicardial fat, the vasa vasorum of the pulmonary artery and aorta, the vessels of the pericardium, diaphragm, mediastinum and pleura.[36] (3) Coronary-luminal anastomoses.

The importance of these anastomoses lies in their potential capacity as a collateral source of blood for areas of heart muscle deprived of an adequate blood supply by the narrowing or occlusion of a coronary artery. Studies at autopsy of hearts treated with injections of colored and radiopaque solutions[56] or radioactive labelled erythrocytes,[51] and then examined radiologically, indicate that the intercoronary anastomoses are the most important source of a collateral circulation and that the right ventricle has a richer coronary anastomosis than the left.[49] In the normal heart, these anastomoses carry a small but significant blood flow while in the presence of coronary narrowing and occlusion, they increase considerably in size and are capable of maintaining a substantial circulation.

The importance of *slow occlusion* in permitting the development and enlargement of anastomotic vessels was demonstrated by the experiments of Gregg, Thornton and Mautz,[32] who produced gradual but complete obliteration of a major coronary artery by successive operations. They observed not only the striking evidences of a collateral circulation but also that the area supplied by the gradually occluded vessel was not infarcted, unlike that

supplied by an artery which is occluded suddenly. Burchell[7] was able to occlude all three main coronary arteries in dogs by gradually constricting them with metal collars anchored to the chest wall. In these instances no infarct developed because of a collateral circulation from branches of the coronaries proximal to the occlusion. In human instances of coronary arteriosclerosis, coronary artery occlusions are observed without infarctions, presumably due to the development of an adequate collateral circulation during the period of coronary narrowing.[56, 5] Infarction often occurs only following multiple occlusions which obstruct the collateral as well as the original blood supply.

Other anastomotic channels are of secondary importance. Prominence of the extracoronary anastomotic vessels following syphilitic obliteration of both coronary ostia[44] suggests that these vessels become significant when the intrinsic coronary vessels have been excluded from the aortic circulation. The importance of these extracoronary vessels may be enhanced if they can be successfully utilized in the surgical production of a collateral circulation in patients with coronary artery occlusion (p. 398). The thebesian and other luminal vessels have also been credited as a means of nutrition to the heart muscle by a reversal of blood flow from the cardiac chambers. But in the left ventricle these luminal vessels are insignificant, while in the right ventricle venous blood would be supplied. There is no satisfactory evidence that the heart is ever nourished by way of the luminal vessels[63, 27, 49] except possibly the superficial endocardium. Another suggested means of collateral circulation is arteriovenous channels. By connecting eventually with capillaries these could serve as a shunt to provide oxygenated (arterial) blood even after occlusion of a coronary artery.

Disagreement as to whether or not the coronary arteries are end arteries is due chiefly to differences in definition of the term. Experimental and pathologic observations have demonstrated that they are not end arteries, anatomically, since there are abundant intercoronary and extracoronary anastomoses. However Blumgart et al.[5] by their method of injection of radiopaque lead agar mass found that the anastomotic communications in normal hearts did not exceed 40 micra in diameter and were relatively insignificant for collateral blood flow. More recently Prinzmetal and associates demonstrated that a radiopaque gelatin mixture injected into one coronary artery appeared in the opposite artery,[50] that glass spheres 70 to 80 micra in diameter were similarly recovered,[51] and that human red cells tagged with radioactive phosphorus (P^{32}) and perfused through one artery appeared throughout both ventricles.[51] Thus collateral channels 70 to 80 micra in diameter, or the size of arterioles, are encountered in normal hearts while even larger communications up to 150 micra in diameter are found in hearts with coronary artery narrowing or occlusion. Nevertheless this confirmatory evidence of abundant anastomoses does not negate the essential fact that coronary occlusion is usually followed by myocardial infarction, i. e., that the available collateral vessels are inadequate to maintain myocardial viability. This is the basis for the statement that the coronary arteries are physiologic but not anatomic end arteries.

CORONARY BLOOD FLOW AND ITS CONTROL

Cardiac Output and Coronary Blood Flow. Studies on the heart-lung preparation of the dog revealed a coronary flow of 50 to 75 cc. per 100 gm. of

heart per minute.[16] Essentially similar values were more recently obtained (a) by measuring the coronary inflow with a bubble flow meter,[10] and (b) by the Fick principle, with the aid of the nitrous oxide method and catheterization of the coronary sinus.[9, 4a] According to these measurements the coronary arteries receive 5 per cent of the cardiac output.

The coronary blood supply must be considered, not only in terms of its absolute value, but always in relation to myocardial requirements. There is evidence that in the innervated heart the coronary flow is adjusted to myocardial needs, and varies with the output and work of the heart. In this respect it resembles other organs in which the vascular bed enlarges and the blood flow increases with heightened activity of the organ. In dogs performing strenuous work on a treadmill the maximal sustained coronary blood flow was 400 per cent of that when the animal was at rest.[12] There was an increase in coronary blood flow up to 84 per cent in the quietly resting dog following the ingestion of a mixed meal.

In denervated hearts there is a reduction in coronary flow when the strength of cardiac contraction is enhanced by augmenting the venous return or increasing aortic resistance.[2, 39] But in the innervated heart-lung preparation[4] and in the intact animal[53, 12, 28] the coronary flow *increases* when the cardiac output is enlarged by augmenting the venous return, by increasing pulmonary resistance[29] or by external cooling of the body surface.[53] The increase in coronary flow is probably due to coronary vasodilatation, effected by inhibitory vagal or other reflexes or by local metabolic changes. These adjustments of coronary blood supply to accommodate an increase in the work of the heart may be greatly impaired when the vessels are the seat of advanced arteriosclerosis.

An increased cardiac rate enhances the coronary outflow by its effect on the cardiac output.[53] For any given increase in cardiac output, the coronary flow increases more when the higher output is due essentially to an increased cardiac rate than when due to an increased stroke output. This is probably related to the greater need for oxygen (lesser efficiency) when an increased amount of cardiac work is accomplished chiefly by a higher rate rather than by a higher stroke output.[61, 20]

Mechanical Factors Controlling Coronary Circulation. The coronary flow varies directly with the motor force supplied by the aortic blood pressure[48, 3] and inversely with the resistance in the coronary bed. Both factors vary throughout the cardiac cycle. The coronary resistance is dependent on (a) the extravascular pressure of the myocardium which is greater during systolic contraction than during diastolic relaxation; (b) the pressure at the outflow orifices of the coronary sinus, cardiac veins and luminal vessels in the cardiac chambers; and (c) the caliber of the small coronary vessels as determined by nervous, humoral or local metabolic factors.

As the aortic pressure rises, the coronary flow tends to increase. One would therefore anticipate a greater coronary flow during systole than during diastole. However, the higher systolic aortic pressure is more than offset by the increased coronary resistance, due to systolic cardiac contraction which compresses the intramural coronary vessels. This compression is minimal in the atria, and much less in the right ventricle than in the left. Furthermore in the left ventricle the highest pressure is in the subendocardium and least in the subepicardium. Thus the systolic diminution in coronary flow affects predomi-

nantly the left ventricle and particularly its subendocardial region. This may be a factor in explaining the greatest susceptibility of these regions to myocardial infarction, after coronary occlusion, and to focal necrosis with lesser degrees of coronary insufficiency.

The net effect of the variations in aortic pressure and coronary resistance during the cardiac cycle is to cause a retardation of flow with the onset of isometric contraction, an increased flow as the aortic pressure rises during systolic ejection, and a rapid acceleration of flow during diastole, because the reduction in coronary resistance from myocardial relaxation is proportionally more than the fall in aortic pressure.[67, 23, 52] The total diastolic flow is greater than that during systole partly because of the longer duration of diastole and partly because of the relatively insignificant intramural coronary compression during diastole.

These considerations suggest that the coronary blood flow would be greatly reduced in cases of aortic insufficiency and arteriovenous aneurysm, in which the diastolic pressure is quite low. However, there are at least two compensatory mechanisms: (1) the systolic pressure in these conditions is often sufficiently elevated to make the mean blood pressure normal, despite the low diastolic pressure. (2) The diminution in diastolic coronary flow is offset considerably by a concomitant increase in systolic flow, due to a lowering in peripheral coronary resistance, relative to the systolic pressure.[21, 24] On the other hand, in cases of aortic stenosis, a deficiency in coronary blood flow may result from a sharp reduction in systolic flow.[21, 24] A significant fall in aortic pressure, such as accompanies shock states, may cause a sufficient diminution in coronary blood flow to produce myocardial necrosis.[18]

Physiological variations in coronary blood flow, such as occur with activity, digestion, etc., are determined chiefly by variations in coronary resistance and only slightly by changes in aortic pressure. The coronary resistance is usually altered by changes in coronary caliber and not significantly by changes in intravascular pressure or in intracardiac pressure at the mouths of the coronary sinus or other venous channels. However, in cases of aortic stenosis, heightened intravascular pressure may be the important factor in increasing coronary resistance and diminishing coronary blood flow, while in cases of right heart failure, a pronounced rise of pressure in the right atrium and ventricle may interfere with venous drainage and increase coronary resistance.

Nervous Control of the Coronary Circulation. There is histologic evidence that the coronary arteries are supplied with parasympathetic (vagal) and sympathetic fibers (via the stellate ganglion).[68] The action of these nerves on the coronary vessels and their importance are disputed. Most observers have found evidence that vagal stimulation causes constriction, and sympathetic stimulation causes a dilatation of the coronary arteries[4, 53, 12, 57, 30] in contrast with the vasomotor effect of these nerves on other systemic vessels. It is probable that the vagus and sympathetic nerves modify the basic coronary flow by their effects on the work and consequent oxygen requirements of the heart, more than by their direct effect on the caliber of the coronary vessels.[19] There is experimental evidence suggesting that carotid sinus reflexes[35] and reflexes from peripheral nerves[26] may also modify the coronary blood flow, but their importance is uncertain. It is probable that the vasomotor control of the coronary arteries in man, like that of the cerebral and pulmonary vessels, is relatively weak.

Chemical Control of Coronary Circulation. Effect of Ischemia. In the heart-lung preparation,[34] in the isolated heart,[41] and in the intact animal[28,25] temporary occlusion of a coronary artery, for as little as five seconds, is followed by a pronounced increase in coronary blood flow. The augmented coronary flow is due to coronary dilatation, which may be of reflex origin or due to the local accumulation of acidic metabolites in the anoxic myocardial tissue.[34, 17] Such a mechanism might serve to adjust coronary blood flow to myocardial needs whenever myocardial ischemia occurred, whether as a result of coronary narrowing, increased cardiac work, or a diminution in the oxygen or thiamine content of the coronary blood.

Effect of Drugs on the Coronary Circulation. Many experimental studies have been made on the effect of drugs on the coronary circulation,[42, 15, 22] but the results of these observations, often contradictory, cannot be literally applied to clinical usage in humans.

The *nitrites* increase the coronary flow by effecting a coronary dilatation, proportionately greater than the reduction in aortic pressure.[42, 6] From the clinical therapeutic viewpoint, these are the only unequivocal coronary dilators. In addition, papaverine,[47] the xanthine drugs,[6] especially aminophylline,[62] epinephrine, ephedrine, atropine,[13] thyroxin and coramine (nikethamide) cause an increase in coronary blood flow.

While epinephrine increases the coronary flow,[66] it may increase the work of the heart and the myocardial need for blood to an even greater extent, thus resulting in relative myocardial ischemia. This disparity could account for the occurrence of cardiac pain when epinephrine is given to patients with angina pectoris.[45, 38] It is also possible that the coronary vasodilator action of epinephrine may be slight or absent in patients with arteriosclerotic coronary arteries while its action to increase cardiac work remains as in normal individuals. Epinephrine production may be concerned in the production of angina pectoris by exercise, emotion, cold and hyperinsulinism (hypoglycemia).

The effect of digitalis on the coronary blood flow is varied under different experimental conditions. In trained, unanesthetized dogs, no change in coronary blood flow was observed with full therapeutic doses of digitalis.[14, 8] But the influence of digitalis on the coronary blood flow of patients with congestive heart failure may be otherwise, since the action of digitalis on the cardiac output is not the same in normal subjects and in those with heart failure (p. 174).

Quinidine does not appear to affect the coronary blood flow. Pituitrin, or more specifically its pressor component pitressin, causes pronounced coronary vasoconstriction and a diminution in coronary flow.[15] Calcium and sodium are coronary dilators. Potassium is also a coronary dilator when given in concentrations similar to its concentration in the blood. But potassium is a strong coronary constrictor when given in higher concentrations.[46]

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15

VARIETIES OF CORONARY ARTERY DISEASE

Disease of the coronary arteries may be due to a variety of causes as follows:

1. Arteriosclerosis
2. Syphilis
3. Rheumatic fever
4. Other infections
5. Periarteritis nodosa
6. Embolism
7. Aneurysm
8. Trauma
9. Congenital abnormalities
10. Thromboangiitis obliterans
11. Medial calcification

For the most part these conditions produce only pathologic anatomic lesions which may be entirely asymptomatic. Clinical manifestations of heart disease may result when these lesions interfere significantly with the vascular supply of a portion of the myocardium or when rupture of a coronary artery and consequent hemorrhage are followed by hemopericardium and cardiac tamponade. Thus a clear distinction must be made between coronary artery disease representing asymptomatic anatomic lesions and clinical forms of heart disease due to coronary artery disease and its resulting myocardial damage.

1. *Coronary arteriosclerosis* is discussed in detail in the succeeding chapter under the heading of arteriosclerotic heart disease (p. 336).

2. *Syphilis of the coronary arteries* is discussed in the chapter on cardiovascular syphilis (p. 818).

3. *Rheumatic fever* is associated frequently with lesions of the coronary arteries, but these are almost always microscopic and not responsible for clinical findings (p. 709).

4. Other Infections. Inflammatory changes of the coronary arteries with granular degeneration, cellular infiltration, atrophy and fibrosis were noted by Wiesel[36] and by Wiesner[37] in a variety of infectious diseases, especially diphtheria and scarlet fever, but also typhoid fever, influenza, pneumonia and pyogenic infections. As a rule the lesions were visible only microscopically and affected the media predominantly. But they occasionally extended to the intima where they were grossly visible as minute slightly elevated yellow plaques. The significance and frequency of these lesions were minimized by Scharpff.[28]

In cases of *typhus fever* the capillaries and arterioles of the heart, as well as of other organs, suffer from severe necrosis and thrombosis,[16] but the larger coronary arteries are not significantly affected (p. 845).

Destructive inflammatory changes in the coronary arteries occasionally result

from general infections with bacteremia, especially in cases of *bacterial endocarditis* (p. 783). The lesions are due to direct bacterial action, but inflammatory changes may also result from bacterial toxins. Bacterial infection of the wall may cause a mycotic aneurysm. Minute infarcts due to bacterial emboli occur in a high percentage of cases.[30]

Tuberculous arteritis involving the small coronary artery branches and arterioles was noted by Gouley and associates[11] in 5 of their 6 cases of myocardial tuberculosis. Most often there was an intimal thickening with little or no cellular proliferation. This led to almost complete obliteration of some small vessels. Occasionally there were intimal tubercles. In one case there was extensive destruction of the large coronary arteries and veins by direct invasion of tuberculous inflammatory tissue.

The lesions of the coronary arteries associated with infectious diseases other than syphilis rarely lead to coronary occlusion. This subject has been discussed by Ophüls[23] and by Benson.[3] In the exceptional cases of occlusion due to coronary arteritis, small vessels are usually involved and no significant myocardial damage results. The clinical symptoms, if any, are overshadowed by the general toxemia and more serious complications of the causative disease. However, in a recent case of Salmonella choleraesuis infection[2] an arteritis with thrombosis caused occlusion of the left anterior descending coronary artery with infarction of the left ventricle. The electrocardiogram showed the classic pattern of anterior wall infarction (p. 445). The coronary arteries were said to be involved in one quarter of the cases of brucellosis studied by Manchester.[20]

5. Periarteritis Nodosa (Necrotizing Arteritis). The coronary arteries are affected in 60 to 70 per cent of that motley group of cases known as periarteritis nodosa.[13, 18] They were involved in 11 out of 15 cases reported by Spiegel[32] which I was able to study personally. The lesions are characterized by inflammation, necrosis and eosinophilic degeneration of the media and adventitia, and a periarterial inflammatory reaction. Often the necrotic wall yields and gives rise to nodular aneurysms. The term periarteritis nodosa as used by Kussmaul and Maier[17] may be applied properly only to those cases in which there are grossly visible circumscribed nodular thickenings of the arteries, but in recent years cases have been included in which there is merely a microscopic necrotizing arteritis and periarteritis (polyarteritis nodosa). Healing may occur with fibrosis of the vessel wall.[4]

Often the inflammatory lesion extends to the intima and may occasionally be complicated by thrombosis. Thrombosis of a large coronary vessel may result in myocardial infarction and a clinical picture resembling that due to acute arteriosclerotic coronary occlusion.[12] I have seen one case in which there was massive infarction of the right atrium. But myocardial infarction is rare, either because the occluded vessel is small or because the occlusion evolves so gradually that an adequate collateral circulation develops. In such cases there may be no clinical symptoms or only those of mild coronary insufficiency; the electrocardiogram may disclose T wave inversions.[18] Hypertension eventually develops in most cases of periarteritis nodosa and may account for cardiac enlargement and electrocardiographic evidence of left ventricular strain. When there are gross aneurysms due to necrotizing arteritis, there are usually no clinical manifestations. Occasionally an aneurysm ruptures and results in hemopericardium which may be fatal. In one case which I observed, this complica-

tion was overshadowed by an associated perirenal hematoma and uremia. In 4 cases which I reported with Gross,[9], the lesions of necrotizing arteritis were accompanied by typical endo-myo-pericardial lesions of acute rheumatic fever.

6. Coronary Embolism. Coronary embolism is relatively rare.[3, 26] Hamman[14] collected 30 reported cases of embolic occlusion of large coronary branches and added 10 additional ones from the pathologic records of the Johns Hopkins Hospital. These undoubtedly represent a small fraction of the actual cases which are unreported in medical literature. The following are the usual varieties of coronary embolism:

(a) Fragments of valve vegetation, usually bacterial.
(b) Blood platelet thrombus.
(c) Fat embolism.
(d) Air (gas) embolism.

(a) The most commonly recognized type of coronary embolism is that associated with subacute or acute bacterial endocarditis. Almost 50 per cent of the cases studied by Hamman[14] fell into this group. A single fragment of friable bacterial vegetation is broken off the aortic or more rarely the mitral valve and occludes a major coronary artery or its ostium. Or occasionally a polypoid vegetation, without being broken, is floated against a coronary ostium which it occludes. In either circumstance, sudden or even instantaneous death usually occurs if the embolus occludes a major artery but sometimes the survival period is long enough for the formation of a myocardial infarct, bland or septic.

In the first case of clinically diagnosed acute coronary occlusion recorded by Hammer[15] in 1878, the occlusion was probably due to bacterial embolism of the coronary artery arising in bacterial vegetations of the aortic valve and sinus of Valsalva. In this case diagnosis was possible because the patient lived for forty hours after the occlusion. Provided death is not immediate, infarction follows the embolic occlusion of a single, large coronary branch more often than when the occlusion is due to thrombosis in an arteriosclerotic vessel. In the latter instance the complete occlusion is preceded by a long period of partial obliteration which permits a functionally significant anastomotic collateral circulation to develop. Rarely, when a coronary ostium is blocked by a polypoid vegetation, the occlusion may be intermittent with consequent intermittent attacks of cardiac pain.

As a rule, bacterial emboli are multiple and of minute size and reach the small coronary arterial branches or arterioles. These produce numerous scattered small infarcts and focal inflammatory lesions, which may result in miliary abscesses (p. 807). In occasional instances the bacterial emboli produce a small subepicardial myocardial abscess which may rupture into the pericardial cavity and give rise to a clinically recognizable pericarditis.

(b) Next in frequency are coronary emboli consisting of bland blood thrombi. These arise in thrombi deposited on aortic arteriosclerotic plaques in the sinus of Valsalva or immediately above it, in mural thrombi on the left side of the heart, in thrombi of the coronary arteries, or in peripheral venous thrombi. The mural thrombi at the root of the aorta may themselves block a coronary ostium or give rise to a major coronary embolus or both. As a rule these thrombi are situated on arteriosclerotic plaques but occasionally the underlying disease is due to syphilis, as in the cases reported by Porter and Vaughan.[25] In most of the reported cases, the patients were males between

twenty-five and thirty-five without clinical evidence of cardiac disease, in whom death occurred suddenly.

Mural thrombi of the heart are found frequently in patients with heart disease, especially in those with severe coronary sclerosis and occlusion. Those on the left side of the heart may give rise to one or two emboli of major coronary branches or numerous emboli in small branches. Myocardial infarction with its distinctive clinical picture is more frequent in the reported cases of embolism from mural thrombi than in coronary emboli from other sources. However, in at least some of these, the infarction probably resulted from a local coronary thrombosis, the mural thrombi were secondary, and the latter only terminally gave origin to the emboli. Mural cardiac thrombi give rise to coronary emboli much more rarely than to cerebral or other visceral emboli; the latter lesions usually determine the clinical picture. When numerous small coronary emboli arise from mural thrombi, they may produce multiple small infarcts with eventual extensive myocardial fibrosis and heart failure.[14]

I have several times seen coronary emboli in the same branch with, but distal to an autochthonous thrombus of a large coronary artery. The frequency of such an association is probably greater than is reported. Presumably the embolus arises from the coronary thrombus at a time when it has not yet completely occluded the vessel. The clinical picture is determined usually by the thrombus, not the embolus, because the latter occludes the distal part of the vessel or a small branch.

Peripheral venous thrombi give rise to coronary emboli only in the presence of a functionally patent foramen ovale, since the embolus must cross from the venous to the arterial side of the circulation (paradoxical or crossed emboli). Pulmonary emboli are usually present at the same time. The paradoxical emboli occlude the cerebral vessels much more often than the coronaries. Definite instances of coronary emboli arising from a pulmonary vein have not been reported. In instances of pulmonary suppuration or neoplasm, emboli may arise from an affected pulmonary vein and cause cerebral abscess or metastasis, and perhaps very rarely coronary embolism.

Both the pathologic and clinical diagnosis of these forms of coronary embolism is difficult. In the bacterial form, the pathologic diagnosis can usually be made by demonstrating the source of the embolus in the valvular vegetations, the similarity of structure of the embolus and bacterial vegetation, and the relative normalcy of the coronary wall in the vicinity of the embolus. The pathologic distinction between bland blood clot, coronary emboli and thrombi is more difficult. Again a source must be demonstrated and, if possible, a relatively normal coronary vessel wall. But sometimes emboli are associated with coronary arteriosclerosis and thrombosis.

The clinical diagnosis is rarely made but may be suggested when death occurs instantaneously, in cases of bacterial endocarditis. Sometimes, however, as in 3 cases reported by Garvin and Work,[10] death occurs more or less gradually; in 2 of them there was septic myocardial infarction, 1 with distinctive clinical and electrocardiographic features. When coronary embolism is not promptly fatal, and associated with clinical evidences of myocardial infarction, it is usually indistinguishable from arteriosclerotic coronary occlusion, even when it occurs in a young person.

(c) *Fat embolism* of the coronary arterioles and capillaries is discussed else-

where (p. 885). Either there are no clinical consequences or they are overshadowed by the manifestations of pulmonary fat emboli.

(d) *Air embolism* of the small coronary vessels is also discussed later (p. 886). It is uncertain whether the air emboli in the coronary vessels are responsible for any of the clinical manifestations; the latter are usually due to emboli in the cerebral and pulmonary vessels.[25a]

Rarer forms of coronary emboli have been observed. Thompson and Evans[34] reported a case of solid tumor emboli in both coronary arteries, arising from a malignant teratoma of the testes, which had entered a vein and crossed to the arterial side (paradoxical embolism) by way of a patent foramen ovale. A mass of tumor tissue was seen projecting through the latter. Merkel[21] reported the occlusion of a coronary artery by Plasmodium falciparum with resulting myocardial infarction.

7. Coronary Aneurysms. Aneurysms of the coronary arteries are rare. They are believed to be due to: (a) periarteritis nodosa (necrotizing arteritis), (b) bacterial endocarditis or other generalized bacterial infections, (c) arteriosclerosis, (d) congenital abnormality, and in isolated instances to syphilis,[31, 24] trauma or rheumatic fever. Dissecting aneurysm of the aorta may extend into the coronary artery[35] or involve its orifice.[19] The most frequent cause is probably periarteritis nodosa, the pathology and clinical manifestations of which were noted above. In these cases the aneurysms are often multiple and involve several branches.

Excluding this type, Packard and Wechsler[24] collected 29 cases from the literature and added one of their own; subsequent reviews have brought the number up to 47.[6, 29] The aneurysms were three times as common in males as in females. In the majority, the aneurysm was single and involved the first inch of the left coronary artery. However, aneurysms of the right coronary artery may have been more readily overlooked, although several instances have been reported.[7]

Bacterial (mycotic) aneurysms arise either by bacterial embolization or more often by direct implantation of bacteria, without embolic vegetation, on the intima. A secondary necrotizing or suppurative arteritis with weakening of the wall leads to aneurysm. Such aneurysms are much more frequent in other vessels, especially the cerebral.

Arteriosclerotic aneurysm of the coronary artery is the commonest form after the age of fifty.[22] Usually the aneurysm is associated with coronary sclerosis and narrowing. In Eliasoph's case,[8] a thrombosed aneurysm of the anterior descending branch of the left coronary artery was found proximal to a thrombus in that vessel. He suggested that the aneurysm resulted from two factors: a weakened necrotic patch in the vessel wall, and increased local intravascular pressure which followed occlusion of the vessel distal to the site of aneurysm.

In 25 to 50 per cent of the last two groups, the aneurysm ruptures and causes sudden death due to hemorrhage or hemopericardium and acute tamponade. The rupture usually occurs first into the periaortic space and thence into the pericardial sac. In the arteriosclerotic cases associated coronary thrombosis and congestive heart failure are equally common causes of death.[29]

8. Traumatic lesions of the coronary arteries are discussed in Chapter 45.

9. *Congenital coronary lesions* (p. 679).

10. Thromboangiitis Obliterans. Although the incidence of coronary disease

and coronary occlusion in cases of thromboangiitis obliterans is said to be higher than is usual for the age group affected,[1] no indubitable case of thromboangiitis obliterans involving the coronary arteries has been reported. However, Saphir[27] in a review of 30 cases of thromboangiitis obliterans from the literature, with special emphasis on the coronary changes, reported 1 case in which he stated that the characteristic abnormalities seen in the extremities were also present in the coronary arteries. These consisted of acute inflammation of all the layers of the vessels, including veins as well as arteries, miliary lesions with accumulations of polymorphonuclear leukocytes, histiocytes and giant cells, and thrombus formation. Lesions of coronary arteriosclerosis were found associated with these inflammatory changes.

The patient, a thirty-five year old male, after suffering for six years from the characteristic symptoms of intermittent claudication, suddenly collapsed and died instantly. Necropsy examination revealed multiple small cardiac infarcts and myocardial fibrosis, in addition to the coronary lesions.

11. Medial calcification of the coronary arteries with fibroplastic proliferation of the intima,[33] also described as medial coronary sclerosis,[5] apparently constitutes a distinct pathologic condition. All the cases involve children less than twenty-seven months old. There is an equal distribution between the sexes. The media of the larger coronary arteries are extensively involved and the intimal proliferation may be sufficient to occlude the artery. The cause is unknown, but in some cases there were also severe renal lesions. The lesions may be due to metastatic calcification as in cases of renal rickets, hyperparathyroidism, etc.

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16

CORONARY ARTERIOSCLEROSIS. ARTERIOSCLEROTIC HEART DISEASE

Arteriosclerosis is by far the commonest lesion of the coronary arteries. Sooner or later, in varying degree, most hearts are thus affected. But only in the minority of cases does coronary arteriosclerosis evoke significant myocardial lesions or clinical disturbances of the heart. For this reason coronary arteriosclerosis and coronary sclerosis are undesirable terms when used to express a clinical form of heart disease.

To obviate this confusion the term coronary heart disease has been suggested to represent clinical heart disease due to lesions of the coronary arteries. But this is satisfactory usage only if it is recognized that the cardiac disease may be due to other coronary disturbances besides coronary arteriosclerosis, e. g., syphilitic coronary ostial stenosis. I prefer to retain the term arteriosclerotic heart disease to designate the various clinical cardiac manifestations due to coronary arteriosclerosis and its anatomic cardiac sequelae. However, the degenerative atheromatous, sclerotic and calcific alterations of the endocardium and valves should not be classified as or confused with arteriosclerotic heart disease. They are essentially purely pathologic lesions, the nature of which can clearly be indicated by terms which do not include the words, heart disease.

This chapter encompasses a general survey of the subject of arteriosclerotic heart disease. Angina pectoris, coronary thrombosis and myocardial infarction are almost always intrinsic elements of arteriosclerotic heart disease, but they require sufficiently detailed discussions to justify independent chapters, which follow. This segregation should not obscure their relation to the general heading of arteriosclerotic heart disease.

INCIDENCE OF ARTERIOSCLEROTIC HEART DISEASE

Arteriosclerotic heart disease is the commonest form of clinical heart disease beyond the age of forty. With the progressive aging of our population cardiovascular disease is becoming more definitely the dominant cause of death and arteriosclerotic heart disease the major form of fatal cardiac disease.

The most reliable studies of the incidence of arteriosclerotic heart disease are those concerned with well defined manifestations such as angina pectoris or acute myocardial infarction, q. v. (p. 402).

ETIOLOGY OF ARTERIOSCLEROTIC HEART DISEASE

Underlying Cause. *Arteriosclerosis or atherosclerosis of the coronary arteries* and the consequent disturbances in the blood supply to the myocardium compose the underlying cause of arteriosclerotic heart disease. Unfortunately our understanding of the genesis of arteriosclerosis is still inadequate. The theories offered to explain the pathogenesis of arteriosclerosis are discussed below.

Predisposing and Contributing Causes. *Age and Sex.* Both the pathologic lesions and the clinical forms of arteriosclerotic heart disease occur predominantly after the age of forty and with increasing frequency in subsequent decades. However, instances of advanced arteriosclerotic heart disease are not rare before the age of forty.[30, 62, 91]

Arteriosclerotic heart disease is much more frequent among males than among females, but this predominance does not prevail among diabetic patients and is less striking in the presence of hypertension and among subjects beyond the age of sixty.[66, 45] A satisfactory explanation of arteriosclerosis should account for this striking difference in incidence between males and females and the equalizing effect of diabetes and hypertension.

Hypertension is found in about 50 per cent of men and in about 75 per cent of women with arteriosclerotic heart disease.[21, 45] Conversely there is a high incidence of arteriosclerotic heart disease in patients with hypertension.[9, 23] But the frequency of arteriosclerotic heart disease in the absence of hypertension indicates that hypertension is only an accessory or aggravating factor in arteriosclerosis and not a primary cause.

Diabetes. Arteriosclerotic heart disease develops with unusual frequency among diabetic patients and at a relatively earlier age than among nondiabetics.[66] A similar relationship has been noted to familial xanthomatosis with hypercholesterolemia (p. 959). Myxedema, chronic glomerulonephritis and obesity are some of the other conditions which have been said to predispose to arteriosclerotic heart disease.

Heredity. The occurrence of arteriosclerotic heart disease in several members of a family is a common observation. But there are insufficient formal studies and statistical data to justify the conclusion that heredity is an important factor in arteriosclerotic heart disease.

Other Etiologic Factors. Acute and chronic infections are no longer considered important, if concerned at all, in the development of coronary arteriosclerosis.[48] A relationship of lead, tobacco, alcohol and other toxic agents to arteriosclerotic heart disease appears extremely unlikely. The possible significance of race and differences in diet is discussed under theories of arteriosclerosis. There is indirect evidence that obesity predisposes to coronary arteriosclerosis.[30, 85]

For a more detailed discussion of some of the above etiologic factors in arteriosclerotic heart disease see the chapters on angina pectoris (p. 362) and acute myocardial infarction (p. 404).

DEFINITION AND CLASSIFICATION OF ARTERIOSCLEROSIS

The term arteriosclerosis ("hardening of the arteries") refers to a variety of degenerative vascular changes which are best defined by a description of the

pathologic alterations. The changes due to syphilis, rheumatic fever, specific infectious diseases, thromboangiitis obliterans, periarteritis nodosa, lupus erythematosus among others are not included under arteriosclerosis. The latter comprises three groups of lesions:

(1) *Medial calcification* with or without preceding degeneration or necrosis (Mönckeberg's sclerosis[51]). This produces pipestem and beaded peripheral arteries, but does not occlude the lumen or produce significant clinical symptoms.

(2) *Arteriolosclerosis,* which is characterized by endothelial hyperplasia, thickening and hyalinization of the intima and hypertrophy of the media of the arterioles of the kidney and other viscera. These lesions are associated usually with hypertension.

(3) *Atherosclerosis,*[50] which affects chiefly the large and medium sized musculoelastic arteries (aorta, coronary, cerebral, peripheral). It is characterized by intimal thickening due to lipoid atheroma, fibrosis, calcification, necrosis and hemorrhage. This is the type of arteriosclerosis which involves the coronary arteries and is responsible for arteriosclerotic heart disease. Hereafter arteriosclerosis and atherosclerosis will be used interchangeably when referring to arteriosclerotic heart disease.

It is interesting that postmortem examinations have revealed all three types of arteriosclerosis among youthful individuals with diabetes of more than ten years' duration. Reference should be made also to the superficial yellowish lipoid deposits on the intima of the aorta and coronary arteries which appear commonly in the first decade of life and appear to be reversible in youth but may progress to atherosclerosis later in life.

PATHOGENESIS OF ARTERIOSCLEROSIS

Theories of arteriosclerosis are concerned with two general questions, viz.: (1) whether it is an irreversible, immutable process of aging or one due to exogenous or endogenous factors which may be controlled, and (2) whether the primary disease is an intrinsic abnormality in the vessel wall which then predisposes to secondary lipoid change either locally or by imbibition from the plasma, or whether some primary metabolic change, which alters the blood, results secondarily in vascular lipoidosis and other degenerative changes. The latter disagreement stems from uncertainty as to whether the initial lesion consists of degenerative alteration of the intimal collagen or ground substance[80, 4] or of lipoid containing "foam" cells arising in connection with lipoid deposited from the blood stream.[44]

Aging Theory of Arteriosclerosis

This theory supposes that arteriosclerosis is "an inevitable consequence of aging and therefore an irreversible process."[54] In a general way the occurrence, severity and extent of arteriosclerosis, including coronary arteriosclerosis, increase with age.[57] On the other hand coronary and other atherosclerosis is frequently minimal in very old people;[1, 33] in fact the absence of severe atherosclerosis of the coronary and cerebral vessels may be a prerequisite to the attainment of old age. I have examined many hearts of subjects beyond the age of seventy who died at a home for the aged and often observed that the aorta and coronary arteries were remarkably free from significant atherosclerotic change.

Another objection to the aging theory is the occurrence of advanced coronary atherosclerosis in youth, e. g., in postmortem studies of young German recruits during World War I[52] and in young soldiers during World War II.[30, 91] Pulmonary atherosclerosis appears in young individuals dying of rheumatic mitral stenosis or of congenital cardiovascular abnormalities.

Aging fails to explain the sharp difference in incidence and severity of arteriosclerosis among men and women, the reported difference in incidence in different countries, the variations in distribution among the different arteries and the high incidence in association with diabetes, xanthomatosis and myxedema.

The atrophic and proliferative changes usually described as characteristic of aging differ from those seen in arteriosclerosis.[22] The very term aging is a vague concept which involves many unknown elements, some or all of which may be subject to modification or control.

For these various reasons the fatalistic assumption that arteriosclerosis is an inevitable and inexorably progressive process should be abandoned. It is more probable that arteriosclerosis represents a disease process due to definite physical and chemical factors. More fruitful results will be obtained if concentrated efforts are directed toward discovering and mastering these etiologic elements.

Metabolic Theory of Arteriosclerosis

One of the widely held theories of arteriosclerosis relates its origin to a disturbance in lipoid metabolism, and more specifically in the metabolism of cholesterol. Many variants of this theory have been proposed. Aschoff[4] believed that cholesterol and other lipoids entered the arterial intima from the plasma by a process of imbibition and subsequently cholesterol ester and free cholesterol were deposited and retained in altered intimal tissue. Anitschkow,[2] among others, emphasized the primary importance of hypercholesterolemia in the deposition of cholesterol in the intima. Leary[44] assumed that macrophages in the liver and other reticuloendothelial tissues accumulate cholesterol, travel through the blood stream as cholesterol-containing foam cells and penetrate the intima through spaces between the endothelial cells. According to Leary the accumulation and disintegration of these lipophagic foam cells in the intima result in soft lipoidal atheromata which are characteristic of atherosclerosis. According to Winternitz et al.[88] the development of atherosclerosis depends on the presence of intimal capillaries which rupture and give rise to hemorrhages. The extravasated blood is presumed to be the source of the cholesterol which leads ultimately to atheroma and necrotic intimal thickenings. However, the existence of intimal capillaries in the normal vessel is uncertain; it is more probable that they arise secondarily after the atherosclerotic process has been initiated.

More recently Hueper[39] contended that colloidal imbalance in the plasma leads to the precipitation of the cholesterol as a film on the intima. Consequently intimal nutrition by way of the vascular lumen is impaired. This results in subendothelial intimal anoxia, injury and increased permeability of the endothelial cells and the infiltration and deposition of cholesterol from the serum. This theory professes that the initial disturbance in atherosclerosis is one of solution or dispersion of cholesterol in the blood, due either to hypercholesterolemia or alteration in other substances in the blood which diminish the

solubility of cholesterol. This concept is based in part on the experimental production of atherosclerosis not only by cholesterol but also by polyvinyl alcohol, methyl cellulose and similar macromolecular substances which impair the plasmatic colloidal equilibrium.

Evidence for Metabolic Theory. The metabolic theory is based chiefly on:

(1) Pathologic and chemical studies of the atherosclerotic lesions.

(2) Experimental production of atherosclerosis by feeding cholesterol.

(3) Frequency and severity of atherosclerosis in association with diseases accompanied by hypercholesterolemia.

(4) Purported rarity of atherosclerosis among people whose diet contains little or no animal fat (cholesterol).

1. Pathology and Chemistry of Atherosclerotic Lesions. Pathologic and chemical studies of atheromatous lesions have emphasized the presence of large amounts of lipids, notably cholesterol esters and free cholesterol.[87] The quantity exceeds that which can be explained by local degeneration.[69] The concentrations of the various lipids correspond closely with their concentration in the plasma, suggesting that they reach the intima by nonselective infiltration or imbibition from the plasma.[82, 37] Pathologic observations strongly suggest that the baneful consequences of atherosclerosis are largely due to the deposits of cholesterol in the intima and the secondary reactions to its presence (p. 415).

2. Experimental Atherosclerosis. Atheromatous vascular lesions closely resembling those of human atherosclerosis have been produced experimentally in rabbits by feeding large quantities of cholesterol or animal fat.[3, 81, 5, 44] A pronounced hypercholesterolemia precedes the development of the atheromatous lesions and is presumed to be the primary disturbance leading to intimal cholesterol deposition.

Many objections have been raised to the validity of applying these experimental observations to the explanation of human atherosclerosis.[26] The rabbit is an herbivorous animal; man is omnivorous. Attempts to produce atherosclerosis by cholesterol feeding in a variety of omnivorous animals have been unsuccessful and the distribution of atherosclerotic lesions in herbivorous animals differs from that in human arteriosclerosis. The rabbit is unable to metabolize and excrete cholesterol as does man and accumulates it in the blood and tissues. The quantity of cholesterol fed to rabbits is proportionately far in excess of that usually taken by man, and the resulting hypercholesterolemia has no counterpart in the majority of cases of human atherosclerosis. However, most of these objections to any analogy between experimental atherosclerosis in rabbits and human atherosclerosis appear to have been overcome by the experimental production of a generalized atherosclerosis in the omnivorous dog by means of daily feeding of cholesterol after modification of thyroid function by thiouracil administration.[76] Atheromatosis produced in chickens by subcutaneous implantation of diethylstilbestrol,[18a] and in the rhesus monkey by maintaining pyridoxine deficiency,[65a] are also said to resemble human atherosclerosis. No relationship between these experimental results and hypercholesterolemia has been demonstrated.

Efforts to discover hypercholesterolemia in humans with coronary or other forms of vascular atherosclerosis have yielded contradictory results.[37, 60] Lande and Sperry[43] found that determinations of plasma cholesterol after accidental death revealed no difference between individuals with extensive atherosclerosis and those without such vascular disease. On the other hand, Davis et al.[24]

observed higher values for blood cholesterol and other lipids in a group of patients with angina pectoris, presumably due to coronary atherosclerosis, than in a group of control patients. But there was considerable overlapping of individual values in both groups. Barker[6] likewise found a higher mean level of plasma lipids in cases of arteriosclerosis obliterans than in normal controls but the range in both groups was essentially similar.

Of possibly greater significance are the findings of Steiner and Domanski[74] who studied the cholesterol levels of 15 patients with coronary arteriosclerosis and of 15 normal subjects at frequent intervals for periods up to two years. In the former group they observed a distinctly higher average serum cholesterol but especially noted that it was inconstant and fluctuated widely, while the values in normal subjects remained relatively constant. Since arteriosclerosis requires a long period of development, isolated determinations of the blood cholesterol may not reflect intermittent variations. Since the normal content of serum cholesterol is close to its saturation point, deposition of cholesterol may follow slight elevations above normal levels. The interpretation of reported values for serum cholesterol is obscured by technical difficulties in the methods for cholesterol determination and by uncertainty as to the range of normal.

Recent studies by Moreton[53] of the physical state of the plasma lipids disclosed that after a fatty meal there was a pronounced increase in the size and number of visible particles containing cholesterol, even though there was only a slight chemical elevation of plasma lipid. A similar increase in the size and number of visible cholesterol-containing particles was observed in the sera of patients with myxedema, xanthomatosis and hyperlipemic diabetes, conditions frequently associated with coronary atherosclerosis. Moreton proposed the theory that the cumulative effect of numerous fatty meals produces transient showers of large lipid particles which are deposited in the arterial intima. The neutral fats and fatty acids are more readily removed and resorbed by macrophages and tissue enzymes than free cholesterol and its esters, which accumulate to form atheroma.

3. Association of Atherosclerosis with Clinical Hypercholesterolemia. The frequency, severity and precocity of coronary arteriosclerosis in diseases associated with hypercholesterolemia add considerable support to the cholesterol theory of atherosclerosis. In the cases of *familial xanthomatosis with hypercholesterolemia* there is an unusually high incidence of angina pectoris, coronary occlusion and death at an early age because of severe coronary atherosclerosis[12] (p. 959). Severe coronary atherosclerosis is a common finding in cases of myxedema, which is characteristically associated with hypercholesterolemia[16] (p. 931).

The etiologic relationship of diabetes to premature and advanced atherosclerosis is discussed elsewhere (p. 951). The frequency of advanced arteriosclerosis in youthful diabetics and atherosclerotic coronary thrombosis in diabetic women in contrast with its infrequency among nondiabetic women are unexplained observations which are among the most important clues we possess to the cause of arteriosclerosis. Rabinowitch[63] and others[31, 83, 70] have associated the high incidence of atherosclerosis among diabetics with hypercholesterolemia in the more severe and poorly controlled cases. But Man and Peters[49] found that atherosclerosis with or without hypertension occurred in 79 diabetic patients whether the blood cholesterol was normal or abnormal.

Premature atherosclerosis in diabetes was formerly attributed to the high

fat diets in the pre-insulin era. But there has been no demonstrable reduction in the incidence or severity of atherosclerotic complications despite the use of high carbohydrate diets and better control of fat and carbohydrate metabolism with insulin. In fact, by prolonging the lives of diabetic patients, such measures permit more of them to survive long enough to become victims of atherosclerosis (p. 951). Nevertheless recent evidence has been presented that among young diabetics who had survived twenty years of diabetes 74 per cent of those incapacitated by atherosclerosis of the heart, eyes or kidneys had repeatedly experienced coma, while only 17 per cent of those without atherosclerosis had experienced coma.[29] The specific metabolic or endocrine factor in diabetes which predisposes to atherosclerosis remains uncertain.

4. Relation of Atherosclerosis to Diet. Studies of the dietary intake in various countries and climates have been interpreted to indicate a higher rate of atherosclerosis among people consuming a diet high in fat than among those on a low fat diet.[78, 67] Snapper[72] commented on the rarity of advanced arteriosclerosis among the northern Chinese, who subsist on cereals and omit animal fats. A similar paucity of arteriosclerosis among the Okinawans[76] and Costa Ricans[84] was attributed to their low intake of cholesterol-containing food. Aschoff[4] reported a sharp diminution in atherosclerosis in Germany following World War I when the populace was ingesting a particularly low fat diet, and similar observations have been made during World War II. These reports on the relation of diet and atherosclerosis are suggestive but suffer from an inadequacy of statistical data.

Mechanical Factors in Atherosclerosis: Intravascular Pressure and Hypertension

Many types of mechanical strain or injury have been credited as initiating, accessory or aggravating causes of atherosclerosis.[42] Intimal damage is said to result from the constant wear and tear on the blood vessels due to the impact of the intravascular blood pressure. Purported hereditary atherosclerosis is viewed as the consequence of an inherited inferiority of the vascular structure in its ability to withstand these strains. The localization of severe atherosclerotic lesions at the bifurcation of arteries and the mouths of branches is said to be due to the greater impact of the blood at these sites. Greater mechanical strain may account also for the predilection of atherosclerosis for the posterior wall of the aorta where there is greater vascular fixation[65] and for the vessels of the lower extremities as compared to the upper. Such forces as tension, vibration, shearing between intima and media, and intimal herniation have been postulated as representing irritant stimuli which damage intimal tissue and provoke proliferation, thickening and secondary atheroma formation.[10, 42] Mechanical intimal injury may be considered as a primary change which predisposes to the deposition of lipid. Or the lipid deposits may be primary while the intimal injury is an accessory factor which is important in determining the localization and intensity of the deposits.

According to Moschcowitz[54] arteriosclerosis may result from the mechanical effects of the normal systemic intravascular pressure acting over a long period of time. Hypertension, representing an elevation of the normal intravascular pressure, accelerates and intensifies the arteriosclerotic process. Even when there is hypertension and arteriosclerosis in the greater circulation, atherosclerosis is usually absent in the pulmonary vessels because, according to

Moschcowitz, the pulmonary arterial pressure is only about one-sixth of the normal systemic blood pressure. On the other hand, pulmonary atherosclerosis occurs commonly in the presence of longstanding mitral stenosis or pulmonary conditions which produce hypertension of the pulmonary circulation.[54] The occurrence of phlebosclerosis in sites of prolonged venous hypertension is also noteworthy.

Endocrine Factors

One of the most striking features of arteriosclerosis is the pronounced predilection for the male sex, especially in the absence of diabetes and hypertension. Any satisfactory theory of atherosclerosis should explain this sex difference. The role of the sex glands is naturally to be considered, but little is known of their possible relation to atherosclerosis. Dock[25] found that the arterial intima of males was considerably thicker than that of females and suggested that this anatomic difference might account for the greater susceptibility of males to arteriosclerosis.

The relation of the thyroid gland is suggested by the frequent association of advanced arteriosclerosis in myxedema and by the inhibition of experimental atherosclerosis in the rabbit when thyroid substance or iodides are administered.[17]

A predisposition to coronary atherosclerosis has been observed in cases of pituitary and adrenal tumors with hyperfunction of the anterior pituitary or adrenal cortex (Chapter 42). In these cases concomitant hypercholesterolemia and hypertension complicate efforts to arrive at an etiologic relationship. The association of arteriosclerosis with diabetes also suggests a possible endocrine role of the anterior pituitary, adrenal cortex or pancreatic islets.

PATHOLOGY OF CORONARY ARTERIOSCLEROSIS

Reviews of the historical development of our knowledge of coronary arteriosclerosis have been presented by Benson[11] and by Long.[47] For a detailed description of the gross and microscopic alterations resulting from coronary arteriosclerosis the reader is referred to Bork,[14] Jores,[40] Wolkoff,[89] Leary,[44] Glomset.[32]

Microscopic Appearance of Coronary Arteriosclerosis

The primary and predominant lesions occur in the intima. There is uncertainty as to the very earliest lesions. According to Klotz,[41] Leary[44] and others the initial change is the presence of lipid-containing macrophages (foam cells) in the subendothelial layer of the intima. Shortly thereafter, if not simultaneously, there are deposits of lipoidal material in the ground substance of the intima as well as in the large mononuclear foam cells. Vacuolar degeneration and swelling of the ground substance and collagen framework of the intima are also observed in early lesions. According to Aschoff[4] these degenerative changes are primary and the deposition of lipids secondary.

Subsequently thickening of the intima results from a proliferation of reactive or reparative connective tissue, from increased deposition of lipids within and outside of foam cells, the formation of new capillaries, calcification, and rarely bone formation. The internal elastic lamella may be displaced and fragmented. Sometimes it disappears while newly formed, delicate elastic fibrils arise in the arteriosclerotic plaque.

The changes which follow the initial intimal lipoidosis and degeneration appear to represent attempts at repair or the consequences of disturbances in nutrition. Normally the intima receives most or all of its nutrition by imbibition from the arterial lumen. The deposition of lipoid and the formation of new collagen to repair the damaged intima result in significant thickening of this layer of the artery. In consequence, imbibition from the lumen, even when supplemented by that from the adventitial vasa vasorum, is inadequate to nourish all portions of the thickened intima. Newly formed capillaries arise in the intima, occasionally from the lumen, but more frequently from the vasa vasorum.[34, 38] From this viewpoint the intimal capillaries represent a granulation tissue type of reparative structure designed to compensate for local nutritional deficiencies.

Subsequent changes appear to be determined by the ability of these new nutritive channels to keep pace with increasing lipoid and other degenerative changes and fibrosis. A deficiency in nutrition results in necrosis of the atherosclerotic plaque. The latter, which is filled with lipid, becomes softened and forms the so-called atheroma, atheromatous abscess or cyst, which is composed of necrotic and degenerative tissue including cellular detritus, cholesterol esters and others lipids. The atheromatous plaque often causes a unilateral thickening of the vessel wall and an eccentric lumen. The atheroma may extend to the surface and rupture through the intima, emptying its contents into the lumen and producing an atheromatous ulcer. Calcium is deposited around the atheromatous focus as well as in the thickened fibrous hyalinized areas of the intima. Large calcified plaques may result and occasionally bone is deposited in or replaces calcified areas. Rupture of the intimal capillaries results in localized hemorrhages which may either advance the arteriosclerotic process by increasing the circulatory insufficiency or, more important, may result in acute coronary occlusion (p. 415). Fibrinoid intimal masses often found in the region of arteriosclerotic plaques may represent compressed and hyalinized elements of the blood due to such hemorrhage.[19]

Changes in the media are much less prominent and consist of atrophy of the muscular and elastic elements. This is probably the result of compression by the thickened intima. The atrophic changes produce thinning and sometimes almost complete disappearance of the medial layer of the artery. Fibrosis and hyalinization of the media are not uncommon in the region of the atherosclerotic plaque. Occasionally lipoid material and calcium may be deposited in the media as well as in the intima. Sometimes capillaries may be seen extending from the adventitia through the media to the basal layers of the intima.

The *adventitial changes* are less striking but frequently irregular patches of fibrosis and focal collections of lymphocytes simulate inflammatory lesions.

Macroscopic Pathology

Mild lesions are represented by superficial yellowish lipoid flecks, streaks or nodules on the intimal surface or by small white patches of fibrous thickening. More advanced lesions cause pronounced thickening and rigidity of the vascular wall and thick lipoid, fibrous or calcified intimal plaques which protrude into and encroach on the lumen. Extreme degrees of narrowing may result, but evaluation of coronary stenosis at necropsy examination should make allowance for postmortem collapse.[77] Extensive calcification of the coronary artery wall

may produce a pipe-stem consistency. The surface may display ulcerations of softened atherosclerotic plaques and blood platelet thrombi may be deposited in such atheromatous ulcers.

The most serious complication of coronary arteriosclerosis is thrombotic occlusion (for pathology, see p. 415). In addition, atherosclerotic aneurysm and rupture occur rarely.[59] Rupture of such an aneurysm may cause hemopericardium and fatal cardiac tamponade.[56]

The Heart in Coronary Arteriosclerosis. As a rule, uncomplicated coronary arteriosclerosis is unaccompanied by significant cardiac lesions unless the degree of narrowing of the vessels seriously impairs the blood supply to the myocardium. In most instances actual occlusion of the vessel accounts for gross myocardial change (for pathology of the heart in coronary occlusion, see p. 415). Under certain circumstances prolonged coronary insufficiency can occur without coronary occlusion and the resultant myocardial anoxia may be followed by focal or extensive areas of subendocardial myocardial necrosis of the left ventricle and papillary muscles (p. 422).

Frequently, severe coronary arteriosclerosis with narrowing but without occlusion is accompanied by fine diffuse fibrosis of the heart muscle, confined essentially to the left ventricle and papillary muscles. Of 37 cases of severe coronary atherosclerosis without occlusion, Clawson[20] observed severe myocardial fibrosis of irregular distribution in 18, slight fibrosis in 17 and none in 2. These lesions are interpreted as fibrous replacement of myocardial fibers which atrophied or degenerated and disappeared as a result of ischemia. The fibrosis is not a result of inflammation and therefore the term myocarditis is inappropriate. Somewhat similar diffuse fibrosis may be observed as a result of longstanding ischemia in calcific aortic stenosis (p. 608) and in cases of malignant hypertension.

The heart is of normal size or slightly hypertrophied in uncomplicated coronary arteriosclerosis. Moderate left ventricular hypertrophy is frequently present because of an associated hypertension. When coronary arteriosclerosis with or without occlusion results in congestive heart failure, pronounced dilatation and hypertrophy of the heart develop[71] (p. 421).

PATHOLOGIC PHYSIOLOGY

Physiologic disturbances of the heart and clinical manifestations result when the atherosclerotic process seriously impairs the coronary blood supply to the myocardium. This may occur in the following ways:

(1) Atherosclerotic occlusion of an artery may lead to infarction of a portion of myocardium. This is discussed below, p. 410.

(2) Occlusion of an artery may result in chronic potential anoxia of a portion of myocardium. The collateral circulation prevents infarction (see under angina pectoris, p. 365).

(3) Multiple coronary occlusions and myocardial infarctions heal but so impair cardiac structure and function as to cause heart failure.

(4) Coronary atherosclerosis and narrowing insufficient in themselves to produce symptoms may cause coronary insufficiency and cardiac decompensation in a preexisting enlarged rheumatic, syphilitic or hypertensive heart.

(5) Extreme atherosclerotic coronary narrowing without occlusion may cause clinical coronary insufficiency when the demands of the heart muscle increase.

(6) Atherosclerotic rigidity of the coronary vessels may impair their ability to adjust in caliber to changing cardiac demands for blood. This is theoretical.

It will be observed that atherosclerotic heart disease, in the clinical sense, results usually from recent or old coronary artery occlusions and to a lesser extent from extreme coronary narrowing without occlusion. Lesser degrees of interference with blood flow are rarely of physiologic or clinical significance.

CLINICAL FEATURES

The clinical features of arteriosclerotic heart disease may be classified into a variety of syndromes, one or more of which may occur in the same patient at the same or different times during the course of the disease.

1. Angina pectoris or cardiac pain.
2. Acute coronary occlusion and myocardial infarction.
3. Left-sided heart failure including cardiac asthma.
4. Combined left- and right-sided heart failure.
5. Heart block and other disturbances in conduction and rhythm.
6. Gastrointestinal and substitution symptoms.
7. Sudden death.
8. Latent or asymptomatic cases.

Angina pectoris and acute coronary occlusion and myocardial infarction are the most frequent and important manifestations of arteriosclerotic heart disease. For this reason special chapters are devoted to their discussion (see Chapters 17 to 21).

Heart Failure. Manifestations of congestive heart failure (Chapter 5) may emerge after a previous history of angina pectoris or myocardial infarction or they may appear gradually or suddenly as the initial symptoms of arteriosclerotic heart disease. Heart failure may be viewed as the result of progressive coronary narrowing and insufficiency or of repeated myocardial infarcts. When heart failure is the initial manifestation, it is assumed either that progressive cardiac damage occurred without preceding acute localized areas of myocardial anoxia or infarction, or that such episodes were clinically asymptomatic or unrecognized. Frequently, acute left ventricular failure (pulmonary edema) develops concomitantly with a clinical episode of acute myocardial infarction or left- and right-sided heart failure develops more or less rapidly after recovery from the attack.

Left-sided heart failure develops earlier and more commonly because the coronary arteries supplying the left ventricle are most affected by atherosclerosis, infarcts are almost exclusively in the left ventricle and because the left ventricle performs more work and has a greater muscle mass and is therefore more susceptible to ischemia. Frequently associated hypertension also contributes to the development of left ventricular failure in cases of arteriosclerotic heart disease.

Dyspnea on exertion or nocturnal attacks of cardiac asthma are the cardinal symptoms. Frequently patients with arteriosclerotic heart disease suffer from angina pectoris as well as heart failure; therefore, cardiac pain and exertional dyspnea or noctural dyspnea may occur in the same patient. Restriction of activity because of the pain may obscure exertional dyspnea. Weakness is a frequent complaint. Orthopnea and cough due to pulmonary congestion are common symptoms with advanced left-sided heart failure. I have several times observed intractable cough as the dominant symptom of arteriosclerotic heart

disease. Right-sided heart failure, including peripheral edema, hepatic enlargement and systemic venous engorgement, often follows and is combined with evidence of left ventricular failure.

Heart block is an uncommon manifestation of coronary atherosclerosis even though the latter, with or without occlusion, is its most frequent cause. Rarely heart block is the first or only evidence of an acute coronary occlusion (p. 453). The heart block may be asymptomatic, it may give rise to palpitation or precordial discomfort or it may be associated with Adams-Stokes syndrome (p. 302). (For a detailed discussion of heart block, see p. 295.)

Bundle branch and intraventricular block (p. 306) are more common and may be associated with auriculoventricular block. The former conduction disturbances do not produce symptoms, but angina pectoris or congestive heart failure is often present. Not infrequently the finding of bundle branch or intraventricular block in asymptomatic persons is the sole clue to the presence of arteriosclerotic heart disease. But other causes of intraventricular block must be considered (e.g., calcific aortic stenosis, gumma, diphtheria, rheumatic fever, tumors or cysts, drugs).

Auricular fibrillation occurs commonly in advanced cases of arteriosclerotic heart disease with congestive heart failure.[15] The occurrence of auricular fibrillation may be the first evidence which leads to the discovery of previously unrecognized arteriosclerotic heart disease. Premature beats are common but not characteristic of this disease.

Digestive disturbances may be prominent symptoms of arteriosclerotic heart disease. The resemblance of acute myocardial infarction to an acute attack of indigestion is well known. Gaseous eructations may accompany or follow paroxysms of angina pectoris. The development of digestive disturbances predominantly on exertion should suggest coronary insufficiency. Postprandial abdominal fullness, meteorism, belching and flatulence may be due to chronic cholecystitis or functional digestive disturbances, but may also result from arteriosclerotic heart disease. It is sometimes difficult to distinguish the epigastric and substernal pain of angina pectoris from that of peptic ulcer. Both peptic ulcer and chronic cholecystitis are not uncommonly associated with arteriosclerotic heart disease. Digestive disturbances in this type of heart disease may also be due to heart failure (p. 76) or to overdosage with digitalis (p. 189).

Sudden death (p. 229) is due most commonly to arteriosclerotic heart disease, if accidents and poisonings are excluded. It is a common termination in cases of angina pectoris and is often associated with acute coronary occlusion (p. 457). But sudden death may complicate arteriosclerotic heart disease without the occurrence of an acute occlusion.[64] Coronary atherosclerosis with pronounced coronary narrowing but no occlusion or infarction was observed by French and Dock[30] in many cases of sudden death in young soldiers. Under the heading of acute fatal coronary insufficiency Levy and Bruenn[46] described a series of hospitalized patients with arteriosclerotic heart disease who died suddenly and who at postmortem examination presented coronary atherosclerosis, but no fresh occlusion or other anatomic lesion to explain the immediate cause of death. They observed an 11.8 per cent incidence of sudden death in a group of patients with coronary sclerosis without thrombosis as compared with 33.3 per cent in a similar group with coronary thrombosis. Sudden death occurred in 27.5 per cent of those patients who presented a history of

cardiac pain and in 9.1 per cent of those without such pain. Sudden death in arteriosclerotic heart disease is usually attributed to ventricular fibrillation, cardiac standstill, acute massive pulmonary embolism or cardiac rupture following acute myocardial infarction.

Finally arteriosclerotic heart disease may be asymptomatic for long periods of time, its presence being indicated by a past history of angina pectoris or myocardial infarction or by electrocardiographic abnormalities (see below).

DIAGNOSIS OF ARTERIOSCLEROTIC HEART DISEASE

The diagnosis of arteriosclerotic heart disease is based most often on a past or present history of acute myocardial infarction or of angina pectoris. Other causes of angina pectoris such as calcific aortic stenosis (p. 607), syphilitic ostial stenosis (p. 821) or extreme anemia are usually relatively easy to distinguish.

In the absence of myocardial infarction or angina pectoris the diagnosis of arteriosclerotic heart disease is always uncertain but may be presumed if manifestations of congestive heart failure, especially cardiac asthma or pulmonary edema, appear in patients past forty-five years of age who present no other apparent cause for these symptoms. Electrocardiographic changes (see below) suggestive of recent or old myocardial infarction lend support to the diagnosis. Attacks of Adams-Stokes syndrome are usually indicative of arteriosclerotic heart disease.

Sometimes a presumptive diagnosis of arteriosclerotic heart disease is justifiable on the basis of routine electrocardiographic findings. The distinctive electrocardiographic abnormalities of acute myocardial infarction (p. 442) are of course diagnostic. Healed infarction may be disclosed by persistent M or W-shaped QRS complexes in lead I or II, by the presence of a large Q and an inverted T wave in lead I or by similar findings in leads II and III, or by low or absent R waves and inverted T waves in precordial leads over the left ventricle.

T wave inversions often denote myocardial impairment due to coronary arteriosclerosis but may be due to a variety of other causes which can often be excluded. S-T interval deviations may be associated. Inversion of T_1 and especially of T_1 and T_2 are much more significant than isolated inversion of T_3. Inversion of the T wave in the precordial leads occurs commonly in arteriosclerotic heart disease and is usually more striking than in the standard leads.[13] Inversion of T_3 is common in obese individuals or as a result of other factors which elevate the diaphragm or produce a transverse position of the heart. Occasionally T_2 as well as T_3 may become inverted as a result of respiratory or postural changes.[68] Inversion of T_1 with depression of ST_1 and left axis deviation is common with severe hypertension[18, 7] and may not necessarily denote arteriosclerotic heart disease. Digitalis causes pronounced T wave inversions and S-T depressions, which are often distinctive (p. 191). T wave inversions due to pericarditis, a variety of acute infections or toxic or nutritional disturbances can usually be differentiated by the clinical history. S-T interval depressions, and/or lowering or inversion of T waves, appearing after an exercise or anoxemia test, are strongly confirmative of arteriosclerotic heart disease (coronary insufficiency) when there is a clinical suspicion of that condition or the clinical features are atypical.

Q waves may be indicative of arteriosclerotic heart disease [28] Often they

persist, with or without T wave inversion, as the residua of a previous cardiac infarction. A large Q_3, often associated with a Q_2, may persist after infarction of the posterior wall of the left ventricle, but a Q wave is often present in lead III in normal individuals. According to Pardee[61] and Durant,[27] a Q_3 is significant of myocardial damage only if the voltage of the Q wave is at least one-fourth as great as that of the tallest QRS complex in any standard lead, and if a Q_2 of at least 1 mm. is also present. Durant[27] found that the significance of a Q_3 as an indicator of arteriosclerotic heart disease was enhanced if: (a) Q_3 was at least half as large as the tallest QR, (b) Q_2 was at least one quarter as large as R_2, and (c) there was no right axis deviation. A Q_3 prolonged to more than 0.04 second is suggestive of arteriosclerotic heart disease.[8] Recently differentiation of normal from abnormal Q waves in lead III has been facilitated by the use of an augmented unipolar left leg lead.[55]

Both with respect to T and ST abnormalities and to the finding of Q waves, their significance in the diagnosis of arteriosclerotic heart disease increases if they disclose progressive change, in repeated observations over a period of months or years.[86]

Conduction disturbances are often suggestive of arteriosclerotic heart disease when they are observed in middle-aged or older individuals and if rheumatic heart disease, syphilitic heart disease, congenital cardiovascular disease, diphtheria and other infections and drugs such as digitalis or quinidine can be excluded as etiologic factors. Such exclusion is often possible on the basis of the history, physical examinations and laboratory tests. Partial or complete heart block may be observed in patients with old and often unrecognized coronary occlusions or in cases of severe but nonocclusive coronary atherosclerosis. Bundle branch block, especially of the left bundle, and intraventricular conduction defects, characterized by widening of the QRS interval to 0.12 second or more and by slurring and notching of the QRS waves, are usually diagnostic of arteriosclerotic heart disease.[58, 35] But rheumatic fever, diphtheria, congenital lesions, quinidine and the Wolff-Parkinson-White syndrome must be excluded. Low voltage, with or without slurring of the QRS complexes in leads I and II, often with low or inverted T waves, is suggestive of arteriosclerotic heart disease if myxedema, constrictive pericarditis and pericardial effusion can be excluded. QRS complexes which are of low voltage, slurred and notched only in lead III, are usually insignificant.

Roentgenologic examination may help in the diagnosis. Occasionally an enlarged cardiac silhouette is the first clue to the presence of unrecognized arteriosclerotic heart disease which is then confirmed by a careful history or electrocardiographic examination. Absence or reversal of left ventricular pulsation, discovered by fluoroscopy, may similarly suggest or add support to a diagnosis of arteriosclerotic heart disease with old infarction and possible ventricular aneurysm. The roentgenogram may reveal calcification of the coronary arteries which appear as linear and segmental streaks in curves corresponding to the course of the vessels.[90] Calcification denotes coronary arteriosclerosis but not necessarily clinical arteriosclerotic heart disease.

Summary of Diagnostic Features. 1. Clinical or electrocardiographic evidence of a recent or past attack of myocardial infarction warrants a diagnosis of arteriosclerotic heart disease.

2. Angina pectoris usually denotes arteriosclerotic heart disease but less common causes of this syndrome must be excluded.

3. Electrocardiographic abnormalities, including T wave inversions and ST deviations, the presence of Q waves and auriculoventricular and intraventricular conduction disturbances often permit a presumptive diagnosis of arteriosclerotic heart disease if due regard is given to the age and clinical history of the patient and if other causes of such electrocardiographic changes can be reasonably excluded.

4. Cardiac enlargement and congestive heart failure in middle-aged or elderly subjects may suggest the presence of arteriosclerotic heart disease but these abnormalities should provoke a careful review of the history and findings on physical and electrocardiographic examination in an effort to confirm the diagnosis or discover other etiologic factors.

Certain misconceptions regarding the diagnosis of arteriosclerotic heart disease should be dispelled. Heart failure or other abnormal cardiac findings are not necessarily due to arteriosclerotic heart disease merely because the patient is past fifty or past sixty years of age; neither does youth exclude this diagnosis. The finding of arteriosclerotic radial arteries or of arteriosclerosis of the aorta, lower extremities, or the retinal vessels does not denote that ateriosclerotic heart disease is also present. Arteriosclerotic heart disease is not excluded because of the absence of physical signs in the heart nor because of a normal cardiac size or a normal electrocardiogram.

PROGNOSIS

The course and prognosis of arteriosclerotic heart diseases[79] has been studied best in connection with its most specific manifestations, viz., cardiac infarction, angina pectoris, heart failure, bundle branch block, and is discussed in detail under these individual headings.

TREATMENT

The treatment of arteriosclerotic heart disease depends essentially on the specific manifestations such as heart failure (p. 160), myocardial infarction (p. 480), angina pectoris (p. 388) or the various arrhythmias. To avoid repetition the reader is referred to these headings.

Theoretically it would be desirable to direct treatment against the basic cause, namely arteriosclerosis. The elimination of animal fats from the diet has been suggested on the basis of the metabolic theory. But it should be recalled that cholesterol can be synthesized in the body from 2 carbon groups (acetic acid) even when no cholesterol is ingested. Weight reduction is recommended, if the patient is obese, because of the greater frequency of severe coronary atherosclerosis in the obese. However, during rapid weight reduction, utilization of the patient's own fat is tantamount to a high fat diet. It is possible that if obesity is eliminated gradually by a moderate reduction in caloric intake with a minimal intake of animal fat, the incidence and severity of atherosclerosis might be minimized. The proper control of diabetes is obviously desirable even though there is uncertainty as to whether coronary arteriosclerosis is more frequent or severe in the uncontrolled diabetic. The use of thyroid, iodides, choline, or sex hormones is theoretical and the rationale is based only on experimental arteriosclerosis in animals.[36, 73] There is no convincing evidence that any of these measures actually prevent, delay or reverse the arteriosclerotic process in humans.

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17

ANGINA PECTORIS

Clinical Features, Etiology and Pathogenesis

The term angina pectoris was introduced by Heberden[51] (1768) to designate a very distinctive "disorder of the breast" attended with "a sense of strangling and anxiety." By using the word angina (strangling) it is clear that Heberden differentiated angina pectoris from multiple forms of chest pains of varied etiology, which were loosely assembled under the heading of *dolor pectoris*. Heberden described angina pectoris as a special disturbance in which the chest pain was of a peculiar modality, and was often accompanied by psychic phenomena, most striking of which was a fear of impending death (angor animi). He noted that the pain generally occurred in paroxysms and that those afflicted with it were seized, usually while walking, especially after a heavy meal, with an insupportable pain over the sternal region which rapidly vanished when the sufferer rested. There was no associated breathlessness. Those subject to angina pectoris were apparently well between attacks, but often died suddenly.

Angina pectoris refers to a symptom-complex and not a disease.[100, 85] However, its occurrence strongly suggests the presence of one of several specific underlying cardiac diseases. It always indicates the same basic physiologic disturbance, probably myocardial anoxia, whatever the underlying disease.

Definition. Angina pectoris is a clinical syndrome characterized by paroxysmal attacks of a distinctive pain or oppression, usually situated retrosternally, radiating commonly to the precordium and left upper extremity and occasionally to other adjacent areas, precipitated by effort and often also by other factors, relieved rapidly by rest or nitrites, and frequently complicated by sudden death.

Certain elements may be atypical but the occurrence of the pain or pressure with effort is an essential element of the syndrome. Of course the pain of angina pectoris may occur at rest but if it does not also occur with effort or cannot be reproduced by bodily exertion the diagnosis of angina pectoris may be questioned. By this definition, angina pectoris applies only to a grave clinical syndrome resulting from paroxysmal relative inadequacy of blood supply to the heart. The pain of angina pectoris is distinguished from the more prolonged and usually more severe chest pain that results from acute myocardial infarction (see p. 426).

CHARACTERISTICS OF THE PAIN OF ANGINA PECTORIS

Location of the Pain. The primary site of the pain during a paroxysm of angina pectoris is usually at or behind the middle or upper third of the sternum.[49]

The term retrosternal is preferable to describe this location because substernal is misunderstood by many to designate the region below the xiphoid process. The pain is usually centered at the level of the third or fourth rib. Sometimes the primary site of the pain is more extensive and includes most of the precordium. Pains that are localized to a discrete area near the cardiac apex or to the left supracardiac region are rarely manifestations of angina pectoris.

Sometimes a patient experiences paroxysms of pain which occur under the same circumstances as angina pectoris but are not located in the anterior chest. The pain may affect the left scapular or interscapular region, the left wrist or other parts of the upper extremities, and rarely even distant structures such as a carious tooth,[86] an inflamed gallbladder or the like. While such pain cannot properly be termed angina pectoris, its paroxysmal occurrence with general bodily effort and its prompt cessation with rest or nitroglycerin suggest that it is due to the same cause and may have the same serious implications, including the possibility of sudden death.

Radiation of the Pain. While the pain may be localized exclusively to its site of origin behind the sternum, frequently, especially when it is severe, it tends to radiate to the neck, jaw and upper extremities. In its most characteristic form, the pain radiates across the precordium to the left shoulder and upper arm, but it frequently extends as far as the elbow, the wrist or the fingers. The pain may reach the shoulder and upper arm and then skip to the wrist or it may radiate to the wrist and fingers alone without involving any other portion of the extremity. Sometimes the pain clearly follows the distribution of the ulnar nerve along the ventral and medial surface of the hand and fingers, but it may also pursue a more diffuse and irregular course.

When severe, the pain may spread to both shoulders or even to both upper extremities. Not infrequently it radiates to the right shoulder, arm or wrist without involvement of the left (contralateral radiation—Libman[84]). The pain may extend to the clavicle, lower neck or throat, jaw and teeth, especially on the left side. Rarely it extends upward to the face, head and scalp. Occasionally the pain of angina pectoris starts in the sternal region and radiates exclusively or predominantly toward the left scapular region. Rarely it radiates downward to the epigastrium or either hypochondrium, distributions observed more commonly with the pain of an acute myocardial infarction. Sometimes the pain starts in the left wrist, arm or shoulder and radiates toward the sternum (inverse radiation—Libman[84]).

Character of the Pain. The pain of angina pectoris may be mild, severe or excruciating, but whatever its intensity it usually has a special or even characteristic quality. It was this quality which led Heberden[51] to designate it by the term angina, meaning strangling. Other descriptive adjectives which have been used are constricting, pressing, boring or expanding. The pain or discomfort has also been described as a sense of a band or vise around the chest or a feeling of tightness. The pain is usually dull, not sharp, sticking or knifelike, and constant, not throbbing. But the pain may be described as burning or as a heartburn, which has led to diagnostic confusion with peptic ulcer or hiatus hernia. Sometimes patients say definitely that there is no pain but only an oppression or a choking or a sense of a weight over the breast bone or a vague indescribable distress.

When there is a sensation of strangling or choking extending from the

sternum to the throat, the discomfort is sometimes confused with respiratory difficulty and may be erroneously interpreted as dyspnea. Often the pain so resembles that of gaseous distention behind the sternum that the patient tries to belch in order to obtain relief.

The pain often has an insistent quality which compels the patient to remain as quiet as possible, even to hold his breath, and if he has been running or walking, to come promptly to rest. This is a special feature of the pain of angina pectoris which is not necessarily related to its severity, for in some of the most intense types of pain such as that associated with ureteral colic, the patient often moves or thrashes about in preference to remaining quiet. Frequently the sensation in the arms, wrist or hands is described as a numbness or weakness, less commonly as tingling. Occasionally, weakness or numbness of the wrists or arms occurs without concomitant retrosternal or precordial pain in patients who at other times present the more complete picture of angina pectoris.

The skin and subcutaneous tissue, including the muscles, of the areas affected by pain may be tender during the attack and even in the intervals between the paroxysms. Vasomotor and trophic disturbances of these hyperalgesic areas, such as blanching and blister formation resembling herpes zoster, have been described.[105] Instances of localized sweating of the shoulder or arm in patients with angina pectoris have been recorded.[101] Occasionally there are evidences of reflex stimulation of the left cervical sympathetic nerve, such as hyperhidrosis of the left side of the face and dilatation of the left pupil.[94]

Certain psychic features often accompany the pain of angina pectoris.[51, 18] The fear of immediate impending death, termed angor animi, is well known. Latham[72] described it as a "sensation of approaching dissolution." This is a pathognomonic diagnostic feature of the attack, although it is often absent. Frequently patients are embarrassed to admit this fear. Careful interrogation, however, often discloses that this was the dominant feature of the attack and the reason for their seeking medical care. The angor animi during the actual paroxysm of angina pectoris should not be confused with the more vague fears of death which torment patients who discover the nature of their disease and learn that it is often terminated by sudden death.

Duration and Relief of the Attack. The attack of angina pectoris usually lasts only a few minutes. Riseman and Brown[113] found that 97 per cent of attacks of angina pectoris precipitated by exertion actually lasted less than three minutes, but that the patient usually greatly overestimated the duration. Such attacks generally subside after a minute or two if the patient rests immediately when the pain begins. On the other hand, attacks which occur with the patient at rest often persist for five to fifteen minutes or up to a half hour, but rarely longer. A mild residual local soreness may not disappear for hours. When severe pain lasts for more than a half hour, the presence of an acute coronary occlusion should be strongly suspected.

The attacks of angina pectoris vary greatly in frequency. Many patients, having learned the maximum activity in which they can indulge without pain, avoid pain completely for long periods by restricting exercise below the critical point. Some patients suffer a single paroxysm of pain early in the day, usually on walking, after which they are able to carry on normal activity without symptoms. Others have only occasional seizures at intervals of days, weeks or months, the intervals depending to some extent on avoidance of the factors

which excite their attacks. Still other patients, less fortunate, experience numerous seizures each day, often without apparent cause, or after some slight activity or even after simple essential physiologic functions.

OTHER SYMPTOMS AND SIGNS

There is usually no dyspnea or respiratory distress, but the patient may complain of being unable to breathe, or he may actually hold his breath. Burns[18] emphasized that: "If there be actual dyspnea present, you may be sure the disease is either not syncope anginosa (i. e., angina pectoris), or that it is a complicated case with effusion in the chest, ossification of the valves or asthma." Belching is common and the passage of flatus occurs occasionally at the end of the attack; these symptoms are usually accompanied by a sense of relief. Occasionally there is a desire to urinate after the attack and there may be polyuria. Dizziness, faintness, and rarely syncope may occur, (syncope anginosa—Gallavardin)[40, 45] but they are not intrinsic elements of the attack. Palpitation is very unusual unless the attack is precipitated by some form of paroxysmal tachycardia.

Physical Signs. It is important to emphasize that there are often no abnormal physical signs in patients suffering from angina pectoris. When the underlying disease is syphilitic aortitis, rheumatic aortic insufficiency or calcific aortic stenosis, the physical signs are those of the underlying disease (q. v.). In patients with an underlying coronary disease, hypertension is frequent and there may be corresponding physical, roentgenologic and electrocardiographic evidences of left ventricular enlargement (Chapter 3). In patients with previous myocardial infarction there may be electrocardiographic changes and physical and roentgenologic signs of myocardial disease or of ventricular aneurysm.

The *blood pressure* between attacks may be normal but is often elevated. Hypertension was present in 44 per cent of Riseman and Brown's[114] cases of angina pectoris. During the attack there may be a rise in blood pressure[76] but as a rule the blood pressure does not change. The cardiac output, circulation time and venous pressure are normal.[2] Usually also the *pulse rate* is unaltered during the attack, but this is variable.[39] A rise in blood pressure and a rapid cardiac rate are essential features in the unusual attacks of angina pectoris occurring in certain patients with aortic insufficiency[124, 82, 32] (p. 591).

The basal metabolism was depressed in 40 per cent of Riseman and Brown's[114] cases of angina pectoris, ranging between 11 and 25 per cent, but there were no clinical evidences of myxedema. In 60 per cent of these cases the blood cholesterol was elevated above 250 mg. per 100 cc. and in 22 per cent it exceeded 300.

The Electrocardiogram in Angina Pectoris. The electrocardiogram of patients subject to angina pectoris may differ during the attacks from that taken in the free intervals. Ordinarily electrocardiographic studies are made while the patient is free from pain; then they are often entirely normal. However, there may be abnormalities of the T and Q waves or of the QRS complexes such as frequently accompany advanced coronary disease with healed myocardial infarcts and fibrosis, or evidence of left ventricular strain if there is an underlying hypertension or aortic valvular disease.

During a spontaneous or induced attack of angina pectoris, the electrocardiogram usually undergoes significant and often characteristic alterations which disappear with subsidence of the attack.[35, 149, 123, 103, 116] The essential

electrocardiographic abnormalities are: (1) a depression of the R-T interval, and (2) diminished amplitude and eventual inversion of the T waves. These alterations occur most frequently in lead I or leads I and II. Sometimes they involve all three standard leads or only leads II and III. (3) In addition Wilson and Johnston[147] stress a pronounced increase in the S deflection in leads II and III. Unlike the changes in acute pericarditis, the ST deviations are depressed during an attack of angina pectoris. In cases of acute myocardial infarction an ST segment depression in lead I or lead III is characteristically associated with a discordant elevation of the ST segment in lead III or lead I, respectively. However an occasional instance of discordant ST elevation and depression, resembling those seen after myocardial infarction, has been reported in cases of angina pectoris.[147, 111]

Only occasionally is it possible to make electrocardiograms during a spontaneous attack of angina pectoris. However, electrocardiographic studies during paroxysms precipitated intentionally by exercise, rebreathing air or breathing air of low oxygen tension have revealed abnormalities similar to those observed in spontaneous attacks (p. 380). These abnormalities may appear even when these procedures do not produce the pain itself.

ETIOLOGY AND PATHOLOGY

A variety of factors may be concerned in producing angina pectoris. They may be classified as: (1) precipitating factors such as exercise, (2) underlying factors such as coronary artery disease, (3) contributory factors such as anemia, and (4) predisposing factors such as age, sex, hypertension, etc.

Precipitating Causes of Angina Pectoris

1. Bodily Exertion. Physical exercise is by far the most frequent and most significant precipitating cause of angina pectoris. Often a patient reports that while running for a bus on his way to work or while walking up a slight incline to the subway station, he suddenly and for the first time in his life experienced a severe oppressive pain behind the sternum which caused him to stop and which so terrified him that he returned to his home. From then on the pain recurred whenever he ran or walked uphill or even on the level beyond a limited distance.

Walking outdoors is the commonest form of bodily exertion producing the attack. Sometimes the patient suffers pain if he walks up the slightest incline, but not at all on the level; or he experiences an attack when he walks rapidly for a half block or more, but he can walk a mile or more without discomfort if he proceeds very slowly. To avoid embarrassment, some patients walk along slowly and stop repeatedly, pretending to be window-shopping. Because of this, the Germans have designated angina pectoris as the *schaufenster krankheit*. For some patients the amount of exercise which can be performed without pain is remarkably constant. Wayne and Laplace,[138] and Riseman and Stern,[115] using a stair climbing test, observed that when repeated examinations were made of a given patient with angina pectoris approximately the same amount of exercise was necessary to induce an attack. On the other hand, some patients find that when an attack has been provoked by exertion they can, after a brief rest period, resume activity without further pain even when the exercise exceeds that which originally induced the attack.

The severity or amount of exertion does not seem to be the sole factor de-

termining the precipitation of an attack. Some patients suffer pain on walking two blocks on their way to work and then are able to perform rather heavy manual work at their occupation indoors without discomfort. It is notable that many sufferers of angina pectoris can avoid an attack on walking if they eat lightly or if they wait several hours after a meal, but experience a paroxysm if they walk only a brief distance soon after a heavy meal. The psychological element of hurry may be an important factor. Walking in cold weather or against the wind may provoke pain, while similar or greater activity causes no symptoms when the weather is warm. Finding that their attacks are more frequent in the winter than the summer, many patients spend their winters in Florida, or other warm climates, thereby greatly reducing or avoiding attacks of angina pectoris.

The occurrence of angina pectoris following bodily exertion depends on the increased cardiac output and the increased work of the heart resulting from exercise. These are associated with a greater demand for oxygen by way of the coronary circulation. We have noted that normally this increased demand is satisfied by physiologic adjustments which increase the coronary blood flow. However, in patients with angina pectoris some underlying disease such as coronary sclerosis, which renders the vessels rigid and narrow, prevents this normal adaptation, so that the increase in coronary blood flow is not proportionate to the increased demand of the heart. When the exercise stops, the coronary flow is again adequate and the attack of angina pectoris subsides. Following this transient myocardial ischemia caused by exertion, there may be an increase in coronary blood flow (reactive hyperemia) which permits the patient to perform, without pain, the activity which had just induced an attack of angina pectoris.

2. Digestion. It has been noted that after a meal, especially if considerable food is ingested, less effort is required to provoke an attack than ordinarily.[137] Since digestion, like exercise, increases the work of the heart, the relative deficiency of coronary blood flow caused by exercise is exaggerated when the exertion follows a meal. Occasionally a heavy meal by itself induces an attack, even though the patient is at rest. In the normal person digestion is associated with an increase in coronary blood flow proportionate to the increased needs of the heart, but this compensation is apparently ineffective in patients suffering from angina pectoris, because of some underlying coronary or cardiac disease.

3. Cold. Like digestion, exposure to cold enhances the probability of an attack of angina pectoris after an amount of exercise which ordinarily is not followed by pain. Exposure to cold produces this effect by increasing the cardiac output and work of the heart and thereby augmenting the need for oxygen.[112] Gilbert and his associates[42] observed a diminution in coronary blood flow in decerebrate dogs, following stimulation of the nasal mucous membranes with ice water. This effect was prevented by previous vagal section or the administration of atropine. They interpreted the reduction in coronary flow as resulting from a reflex in which the trigeminal fibers were stimulated on the afferent arc and the vagi on the efferent, thus producing coronary vasoconstriction. Freedberg and his co-workers[37] reduced exercise tolerance and precipitated angina pectoris by the local application of ice to the hand, presumably causing coronary vasoconstriction. Reflex stimulation of epinephrine with consequent increase in cardiac work could also account for the angina pectoris.[20] Exposure of the

skin surface to cold may rarely induce an attack of angina pectoris, even without the additional factor of exercise. This is observed in patients who experience pain on retiring if the room or bed clothes are very cold, or on stepping into a cold bath.

4. Emotion. While intense emotional states may provoke in neurotic persons various forms of pain in the cardiac area which are distinct from angina pectoris, they may also and often do cause definite attacks of angina pectoris, whether or not there is an associated neurosis. Heated arguments, the excitement of card playing or of watching a football game or a horserace, grief and anger, and a variety of petty annoyances may all induce an attack. Not infrequently cardiac pain occurs during sexual intercourse and rarely the attack is fatal.

Like other factors precipitating angina pectoris, excitement is believed to act by increasing the work of the heart in subjects in whom, because of some underlying disease, the coronary blood flow cannot be proportionately augmented. The increased work of the heart is believed to be effected by the hypersecretion of epinephrine which is associated with emotional states.[19]

5. Tachycardia. When severe tachycardia occurs in paroxysms (paroxysmal auricular fibrillation, paroxysmal nodal tachycardia), it may induce an attack of angina pectoris in persons with a diminished coronary reserve. Rapid heart rates above 160 per minute augment the oxygen consumption of the heart because for any given minute output the oxygen need of the heart is greater at rapid than at slow rates.[129] Coronary flow may be impaired with reduction in the duration of diastole. In patients whose coronary reserve is limited, the added myocardial needs for oxygen resulting from the tachycardia cannot be satisfied through the normal accommodative mechanisms. Then a definite attack of angina pectoris may be induced. In contrast with the paroxysmal form of this arrhythmia, persistent auricular fibrillation is rarely associated with angina pectoris.

6. Hyperinsulinism and Hypoglycemia. In diabetic patients with severe arteriosclerosis excessive insulin dosage may induce attacks of angina pectoris or even of myocardial infarction (p. 410). Similar paroxysms of cardiac pain and associated electrocardiographic changes have been induced by spontaneous episodes of hypoglycemia due to hyperinsulinism (p. 950). The angina pectoris has been attributed both to disturbed cardiac metabolism due to the hypoglycemia and to an increase in the production of epinephrine in response to the low blood sugar.[30, 43]

7. Other Precipitating Causes. Attacks of angina pectoris have been ascribed to the administration of thyroid extract, especially in patients with myxedema (p. 936). It has been indicated that epinephrine as well as insulin may cause cardiac pain.[110] Occasionally tobacco appears to precipitate paroxysms in susceptible individuals.[147, 108, 14] Smoking may produce this effect by increasing the heart rate and elevating the blood pressure.[119, 81]

Many attacks of angina pectoris occur without apparent cause or in the course of ordinary conversation, especially if it is prolonged. Straining at stool is sometimes responsible. Preliminary to an attack of acute myocardial infarction, angina pectoris may increase in frequency and occur with little or no provocation.

Occasionally attacks of angina pectoris are precipitated by the recumbent position, especially at night, and the patient is forced to walk about or sleep

in the sitting position in order to obtain relief. This has been noted particularly in patients with aortic insufficiency and angina pectoris, but I have also observed it in patients with pain due to coronary arteriosclerosis. The term angina decubitus has been applied to this type of cardiac pain, which may be precipitated by emotional factors or by increased cardiac output and work associated with recumbency. However, there has been considerable confusion about this term, which has also been applied to the precordial oppression associated with paroxysmal nocturnal dyspnea and to the pain accompanying acute myocardial infarction.

Underlying Causes of Angina Pectoris

The above-mentioned precipitating factors induce attacks of angina pectoris only in subjects who are susceptible because of some underlying cardiac disease. Since angina pectoris is a symptom complex which may be due to a variety of diseases, a complete diagnosis should include not merely the term angina pectoris but also the underlying causative disease. The basic conditions which are usually responsible for angina pectoris are: (1) coronary arteriosclerosis, (2) syphilitic aortitis, (3) aortic stenosis and (4) aortic insufficiency. Angina pectoris has been associated also with anemias, especially pernicious anemia, with hyperthyroidism and hypothyroidism, tachycardias, hypertension and mitral stenosis. But it is uncertain whether these conditions are basic causes or merely contributing factors in the production of angina pectoris. Not infrequently two or more of the above diseases are combined and may be jointly responsible.

1. Coronary Arteriosclerosis (See also Chapter 16). Coronary arteriosclerosis is by far the commonest pathologic basis of angina pectoris. Either coronary thrombosis or severe narrowing produces pain by interfering with the blood supply of the myocardium. The pathologic findings and their correlation with angina pectoris are discussed below (p. 367).

2. Syphilitic Aortitis with Coronary Ostial Stenosis.[59, 39, 65] This is discussed in Chapter 35. The occurrence of angina pectoris is determined by severe narrowing or obliteration of the aortic mouths of the coronary arteries. The increased myocardial need for blood, due to the enlarged size and work of the heart caused by an associated aortic insufficiency, is a predisposing factor.

3. Aortic Stenosis. Aortic stenosis of the severe variety, so-called calcific aortic stenosis, is often manifested clinically by angina pectoris.[9, 24, 38, 23, 66] Contrary to general belief, angina pectoris is a relatively more common symptom of calcific aortic stenosis than of aortic insufficiency. The incidence and pathogenesis of cardiac pain is discussed elsewhere (p. 607).

4. Aortic Insufficiency. Syphilitic aortic insufficiency is much more apt to be associated with angina pectoris than is rheumatic aortic insufficiency. But in absolute numbers the latter may be more frequent in places where syphilitic aortitis is uncommon. It is probable that angina pectoris is rarely due to the aortic insufficiency per se, even though the low diastolic pressure associated with that lesion would be expected to impair the coronary blood flow[127] (p. 592). Compensatory factors tend to restore an adequate blood supply (p. 325).

In cases of syphilitic aortic insufficiency, angina pectoris is due chiefly to the usually associated coronary ostial stenosis. In cases of rheumatic aortic insufficiency beyond the age of fifty, an associated coronary arteriosclerosis may

be responsible. In both the valvular lesion may be a contributory, but not primary cause, due to the increased work of the heart and the need for a larger blood supply. In some instances an aortic stenosis is overlooked and aortic insufficiency is diagnosed because of the presence of an aortic diastolic murmur. In cases of angina pectoris in young individuals with rheumatic aortic insufficiency, vasomotor or autonomic crises associated with a sharp increase in cardiac rate and blood pressure may be responsible for the pain.[124, 82, 138, 32]

5. Other Causative Diseases. *Anemia.* Among the uncommon causes of angina pectoris, anemia appears to have the clearest relationship to the production of this symptom.[54] Angina pectoris has been reported most often with pernicious anemia,[25] but it has been observed also with secondary anemias of varied etiology.[60] Nevertheless, even with pernicious anemia angina pectoris is uncommon, and in most series of cases has not been noted at all. Willius and Giffen[146] found a history of angina pectoris in 43 or 2.7 per cent of 1560 patients with pernicious anemia. On the other hand Pickering and Wayne[109] reported that 7 of 25 ambulatory patients with severe anemia complained of pain in the chest induced only by exercise and relieved by rest. They suggested that angina pectoris might occur more frequently in patients with severe anemia if they were not stopped by breathlessness, giddiness or intermittent claudication before they exerted themselves sufficiently to produce anginal pain.

In almost all of the reports of angina pectoris associated with anemia in which the hearts were examined at autopsy severe coronary arteriosclerosis or syphilitic ostial stenosis was found.[53, 150] The case reported by Elliot[28] appears to be an exception, but since the heart weighed more than 600 gm. and the anemia was moderate (57 per cent Sahli) the causal relationship of the anemia to the angina pectoris may be questioned. The infrequency of angina pectoris in cases of anemia, the usual finding of advanced coronary arteriosclerosis at autopsy when angina pectoris had occurred during life, and the usually prompt termination of the attacks when the hemoglobin is elevated by transfusions or other therapy, indicate that anemia can predispose or contribute to attacks of angina pectoris, but only when there is an underlying disease which impairs the blood supply of the heart.

Arterial Anoxemia. Angina pectoris is rarely encountered in cyanotic patients with chronic pulmonary disease or congenital heart disease (hypercyanotic angina), the pain occurring with intensification of cyanosis during activity.

Hyperthyroidism and Hypothyroidism. Rarely angina pectoris has occurred in association with hyperthyroidism[75] or with myxedema.[132, 107] Sturgis[132] attributed the angina pectoris in a case of hyperthyroidism to the increased load imposed on the heart by the elevated metabolism, and relief of the attacks following subtotal thyroidectomy to the reduction in basal metabolism. However, the frequency of hyperthyroidism and the rarity of associated angina pectoris suggests that hyperthyroidism is, at most, only a contributory causative factor. It appears likely that the primary underlying cause of angina pectoris in these cases is coronary artery disease.

Coronary arteriosclerosis probably accounts also for the occasional instances of angina pectoris and hypothyroidism, for the latter is often associated with coronary artery disease (p. 931). But despite the frequency of coronary sclerosis, angina pectoris is uncommon in myxedema because the low metabolic rate results in a reduced myocardial requirement for blood. The relationship

of myxedema to angina pectoris is discussed in the chapter on the former (p. 936). Both the appearance and the relief of angina pectoris in myxedema have been attributed to thyroid extract (p. 936).

Mitral Stenosis. Angina pectoris has been noted occasionally in cases of mitral stenosis.[131, 56, 135, 6] Mechanical factors, such as compression of the left coronary artery between an enlarged left auricle and a dilated pulmonary artery, have been invoked to account for the angina pectoris. But considering the frequent occurrence of mitral stenosis and of angina pectoris as separate entities, the comparatively rare coexistence of the two conditions[77] in the same patient must be explained as accidental, not causal, the former being usually due to rheumatic infection and the latter to independent coronary disease.

According to Burgess and Ellis[17] in addition to angina pectoris three other types of chest pain associated with mitral stenosis must be distinguished, none of them directly due to the stenosed mitral valve. The most common is the dull ache or sticking pain, often apical in location, due to cardiac neurosis especially in patients who have been made heart-conscious. The second is the precordial pain and hyperesthesia due to the presence of active rheumatic carditis and perhaps pleuropericarditis. The third is hypercyanotic angina, which is characterized by retrosternal or precordial pain, which may be very severe and last for hours or days but which is not accompanied by fever, leukocytosis or electrocardiographic abnormalities. The pain occurs in patients with mitral stenosis who are severely cyanotic and often suffer from pulmonary edema and collapse. It is relieved by the administration of oxygen. Burgess and Ellis conclude that hypercyanotic angina is due to myocardial anoxia in a hypertrophied heart. In addition to these various forms, chest pain in mitral stenosis may occur in the presence of cardiac failure and auricular fibrillation, due to complicating pulmonary infarcts and pleuritis.

Contributing Factors

These are conditions which favor the occurrence of angina pectoris in subjects who are already susceptible because of coronary disease, syphilitic aortitis with coronary ostial stenosis, or aortic valvular disease. The contributing factors, unlike the basic underlying causes, are by themselves incapable of producing angina pectoris and unlike the precipitating factors do not immediately initiate the individual attacks. These distinctions have not been, and sometimes cannot be sharply drawn. Hyperthyroidism and anemia are two factors which, as I have indicated, may be properly considered as contributory factors in the production of angina pectoris, although they have also been reported as primary underlying causes.

Diabetes predisposes to angina pectoris because of its relation to coronary arteriosclerosis (p. 951).

Hypertension is often found in patients with angina pectoris, but usually the latter may be properly attributed to associated coronary disease. Hypertension is especially frequent in women with angina pectoris (90 per cent or more in some series).[29, 78, 26] Davis and Klainer[26] found an extreme degree of coronary disease, involving two or more major arteries, in 95 per cent of nonhypertensive patients with angina pectoris. Similar severe coronary disease was observed in only 39 per cent of hypertensive patients with angina pectoris. They concluded that if hypertension is present angina pectoris occurs frequently, even in

the absence of severe coronary disease. But in subjects with normal pressure, angina pectoris is almost always dependent on the presence of severe coronary disease. In other words, severe coronary disease may by itself result in angina pectoris; if hypertension is associated, angina pectoris may occur even when the coronary disease is of moderate degree. The hypertension increases the work of the heart and leads to cardiac hypertrophy. Both of these changes increase the requirements of the heart for oxygen. In this way hypertension enhances the likelihood of angina pectoris if there is already some disturbance in cardiac circulation. Similarly, cardiac hypertrophy from any cause may increase the likelihood of angina pectoris. Hypertension contributes indirectly to the occurrence of angina pectoris by favoring the development of arteriosclerosis of the coronary arteries[4, 98] (p. 337).

Familial Xanthomatosis and Hypercholesterolemia (p. 959).

Pheochromocytoma. Angina pectoris is occasionally observed in the rare cases of acute paroxysmal hypertension due to pheochromocytoma (paraganglioma) of the adrenal medulla (p. 945). The sharp rise in blood pressure occurring during paroxysms of hypertension in young patients with aortic insufficiency has been mentioned.

Obesity may contribute to the production of angina pectoris, probably because of the increased cardiac work which it necessitates. A reduction in weight sometimes results in a diminution or disappearance of angina pectoris in obese patients with heart disease.

Focal infections have been reported as contributing to the production of angina pectoris,[128] but scanty data were presented either to support this claim or to indicate an improvement following the removal of active focal infections.

Disease of the Biliary and Gastrointestinal Tracts. The causal relationship of diseases of the gastrointestinal and especially of the biliary tract to angina pectoris has been stressed in recent years. Chronic cholecystitis and cholelithiasis, duodenal ulcer, diaphragmatic hernia and organic and functional disturbances of the esophagus have been documented as causes of angina pectoris. The symptoms of indigestion often associated with the attacks and their relief with eructation and the passage of flatus as the attack abates have suggested that reflexes from the esophagus, stomach, duodenum or colon could produce angina pectoris, perhaps by causing vagal vasoconstriction of the coronary arteries.

This concept was supported by experimental observations that distention of the stomach with balloons decreased the coronary blood flow[27, 41] and that a similar procedure induced angina pectoris in humans.[96] These effects were prevented by previous section of the vagi or administration of atropine. Electrocardiographic changes were observed in humans during experimental distention of the gallbladder.[91] Recently experimental distention of the gallbladder in normal dogs caused no significant electrocardiographic changes, but the same procedure produced marked RST segment deviation and increased height of T waves in dogs which had had a previous experimental coronary artery occlusion.[57] Following a theory postulated by Verdon,[136] the Jacksons[62] submitted experimental and clinical evidence that angina pectoris was caused by acute spasmodic uncoordinated contractions of the esophagus and stomach due to local gas traps and gaseous distention. The theory that disease of the biliary and gastrointestinal tract associated with the distention of these hollow viscera and vagal reflex coronary vasoconstriction can produce angina pectoris

must be distinguished from the fact that normal digestion may precipitate angina pectoris in susceptible subjects. The latter can be explained adequately by the increased work of the heart during digestion independent of reflex action.

The available data suggest that *disease of the biliary tract* is more common in patients who die of coronary disease (and angina pectoris) than in control groups of patients.[13] Yet there is no proof that coronary disease causes gallbladder disease or vice versa, or that a common etiologic factor is responsible for the association. Occasional cases have been recorded in which anginal attacks and electrocardiographic abnormalities disappeared after cholecystectomy.[36] It is probable that in these cases the diseased gallbladder acted only as a contributory cause of pain in the presence of underlying coronary or aortic disease. In many cases of so-called angina pectoris due to gallbladder disease there is a failure to distinguish carefully between the pain radiation of cholelithiasis and cholecystitis and angina pectoris; as a rule the two can be clearly distinguished.[148] Occasionally, common afferent pathways cause the referred pain of biliary disease to simulate that of angina pectoris or vice versa.[93]

Peptic ulcer is more often associated with coronary disease and angina pectoris than is generally recognized but the association may be no more frequent than is to be anticipated from the high incidence of the individual diseases. Sometimes the anginal syndrome appears and recurs simultaneously with the activation of an old peptic ulcer, and disappears when the ulcer is successfully treated.[10] A bleeding ulcer[79] may precipitate angina pectoris in patients with coronary disease because of the induced anemia (p. 973).

Hiatus (paraesophageal) hernia has occasionally caused symptoms resembling angina pectoris.[97, 64, 99] Careful analysis of the character, location, radiation and precipitating causes of the pain usually discloses distinctive differences from that of angina pectoris. Resemblances may be due to the transmission of pain impulses from the esophagus over cord segments which are similar to those carrying pain impulses from the heart. Occasionally hiatus hernia causes chronic esophageal or gastric bleeding and a severe secondary anemia;[117, 121] in such cases the anemia may contribute definitely to the development of angina pectoris.[11, 31]

Predisposing Factors

Age and Sex. At least 90 to 95 per cent of patients with angina pectoris are beyond the age of forty and more than 70 per cent are beyond the age of fifty. Angina pectoris in young persons (below the age of thirty) has, however, been recorded.[44] These young subjects may suffer from rheumatic aortic insufficiency.[143] Eppinger and Levine[29] found the average age of onset of angina pectoris to be fifty-six for males and fifty-eight for females and the range between thirty-five and seventy years.

Angina pectoris occurs predominantly in males, the ratio varying from 3 to 1, to 6 to 1 in different series.[102, 21] As a rule, angina pectoris occurs in females only when there is an associated diabetes or hypertension.[78, 133]

Occupation, Social and Economic Status, and Race. There is a strong clinical impression that while angina pectoris may appear in persons of any occupation, it affects particularly those whose work subjects them to continuous mental tension, such as business managers, executives and professional

men, particularly physicians and lawyers. However no convincing data have been adduced to support these clinical impressions.

Similar uncertainty concerns the relationship of social status to angina pectoris. Angina pectoris undoubtedly occurs in persons of all social and economic strata.

Angina pectoris has long been considered infrequent, if not rare, in the Negro race.[118] In recent years this alleged rarity of angina pectoris in Negroes has begun to appear exaggerated.[139] Perhaps as the Negro has become more and more exposed to the economic and emotional strains of industrialized civilization, he has been more frequently subject to angina pectoris just as he has to hypertension and hyperthyroidism.

Heredity. The most striking predisposing factor in angina pectoris is its familial occurrence. A careful family history, when this is known to the patient, usually discloses that the patient's parents, siblings, etc., also suffered from angina pectoris or other evidence of coronary arteriosclerosis.

Constitution and Temperament. The individual factors which determine this apparent hereditary predisposition are unknown. Aside from the supposed poor quality of the vascular tubing (including the coronary arteries) of certain persons which renders them susceptible to arteriosclerosis, there are also external constitutional characteristics which seem to be associated with angina pectoris. Subjects with this ailment are often short and stocky, overweight, short-necked, with barrel-shaped chest and a high diaphragm. They are often aggressive, ambitious, serious, one-tracked persons with extreme emotional reactions which are either repressed, or expressed in explosive outbursts.

Obesity, diabetes mellitus and *hypothyroidism* are other factors (see also p. 337) which seem to have a more than coincidental association with angina pectoris. These conditions predispose to angina pectoris by increasing the frequency of an underlying arteriosclerosis.

PATHOGENESIS

Although a variety of explanations have been offered for the mechanism of angina pectoris[59] and although there is still some difference of opinion as to its exact pathogenesis, the most widely accepted theory at the present time is that the pain and associated phenomena result from myocardial anoxia, induced by coronary insufficiency.[69]

Coronary Insufficiency. Whenever the coronary blood flow, quantitatively or qualitatively, fails to keep pace with the myocardial needs, coronary insufficiency is said to be present.[16, 80] Coronary insufficiency is thus defined as a disproportion between the blood supply and the blood requirements of the myocardium. Coronary insufficiency may be due to a diminution in coronary inflow, an increase in the size and work of the heart, a deficiency in the oxygen content of the blood, or a combination of these. The following are more specific causes of coronary insufficiency: (1) coronary occlusion, recent or old, (2) coronary arteriosclerosis with narrowing, (3) coronary ostial narrowing or occlusion due to syphilitic aortitis, (4) aortic valvular disease, (5) conditions associated with a reduction in aortic blood pressure, e. g., massive pulmonary embolism and other shock states, (6) conditions associated with a reduction in oxygen content of the blood, e. g., anemia, arterial anoxemia due to pulmonary or congenital heart disease, carbon monoxide poison, or low atmos-

pheric oxygen tension, (7) drugs, e. g., epinephrine administered therapeutically, or spontaneous epinephrinemia in cases of pheochromocytoma (p. 945).

Confusion has resulted from an attempt to limit the term coronary insufficiency to "functional" deficiencies in the coronary circulation, thus excluding mechanical obstructions of the coronary artery, i. e., coronary occlusion. Angina pectoris, which is one of the most striking symptoms of coronary insufficiency, is due more often to old coronary occlusion than to any other cause. Angina pectoris and coronary insufficiency are not synonymous. Coronary insufficiency is a disturbance which under special circumstances may produce angina pectoris and under others, myocardial necrosis or infarction, or it may be documented only by electrocardiographic abnormalities unassociated with pain.

Normally the coronary circulation is adequate for the myocardial needs at any given moment. A wide range exists between the coronary flow under basal conditions and the larger flow when myocardial requirements are maximal. This range may be termed the *coronary reserve*. Under physiologic conditions the coronary flow can be augmented by certain compensatory adjustments which reduce the coronary resistance by dilating the coronary vessels. Under pathologic conditions, the development of a collateral circulation also helps to maintain an adequate myocardial blood supply, but this may not be adequate under all circumstances. When the coronary blood bed is attenuated by narrowing or obliteration of vessels, or when the myocardial needs are increased by cardiac hypertrophy or valvular disease, the range between basal coronary blood flow and maximal coronary blood flow becomes narrowed. There may then be said to be a diminution in coronary reserve.

When the coronary reserve is diminished to the point where the flow is adequate only for ordinary needs, any sudden further depletion of the blood supply or increase in myocardial demands may result in coronary insufficiency. The coronary blood flow may be reduced by a fresh coronary occlusion, by an acute hemorrhage or by a sharp reduction in blood pressure following massive pulmonary embolism, acute pancreatitis, etc.; or the myocardial blood demand may be augmented by bodily exertion, excitement, digestion, cooling of the surface of the body or any other factor which exaggerates the work of the heart. If the coronary insufficiency thus produced is sufficiently severe and prolonged, the resultant myocardial anoxia may be followed by necrosis of an area of heart muscle (myocardial infarction). When, however, the coronary insufficiency is less severe and especially if it is transient, e. g., with physical exertion or excitement, the resultant myocardial anoxia excites only certain temporary metabolic disturbances in the muscle, which are completely or almost completely reversible. Such episodes of acute transient coronary insufficiency are believed to account for the appearance of angina pectoris.

According to this explanation the pain of angina pectoris and that of acute coronary occlusion (with myocardial infarction) are both due to acute coronary insufficiency, the difference in duration and severity of the pain depending on differences in degree and duration of the coronary insufficiency. That the pain of acute myocardial infarction and that of angina pectoris arise similarly from coronary insufficiency (with myocardial anoxia) is supported by: (1) clinical resemblances, (2) electrocardiographic evidences of myocardial impairment in spontaneous and induced attacks of angina pectoris (see below) and (3) the

occasional discovery of foci of necrosis in the hearts of patients who died shortly after having suffered from attacks of angina pectoris.[15]

Some of the confusion in terminology has arisen from a failure to distinguish a pathologic lesion, a physiologic disturbance and a clinical symptom. Coronary occlusion or thrombosis refers to a pathologic lesion. Sometimes acute coronary occlusion is used to denote a clinical picture; then it refers to the symptoms and signs due to the resulting myocardial infarction. Coronary insufficiency is a physiologic disturbance. It may result from recent coronary occlusion, old coronary occlusion, extreme and extensive coronary narrowing, or a combination of these, or from noncoronary cardiac diseases. Angina pectoris represents a symptom or group of symptoms. Its pathologic basis is often recurrent coronary occlusion or progressive severe coronary narrowing. Coronary insufficiency is the underlying physiologic disturbance. Although coronary insufficiency is responsible for both angina pectoris and the clinical picture of "acute coronary occlusion," the two differ in that the myocardial disturbance during angina pectoris is transient, relatively less intense and essentially reversible, as compared with the usually permanent and severe myocardial destruction accompanying acute coronary occlusion. (See also p. 402.)

Pathologic Basis of Coronary Insufficiency and Angina Pectoris. That the mechanism of angina pectoris was in some way related to coronary artery disease has been known since Jenner,[63] Black,[5] Parry,[104] Burns[18] and subsequently others repeatedly found thickening, calcification or obstruction in the coronary arteries of patients who had suffered from this symptom-complex. The relationship was obscured by the frequency with which coronary arteriosclerosis was found in individuals who had not suffered from angina pectoris during life[145, 95] and by the occasional occurrence of angina pectoris in individuals whose hearts disclosed normal coronary arteries at autopsy. On the other hand, Sternberg[130] invariably observed coronary artery disease at autopsy in cases of angina pectoris. Braun[12] reported a series of 127 cases of angina pectoris, in all of which there was severe coronary arteriosclerosis. Usually the narrowing was so pronounced that there was scarcely any lumen.

Most of these discrepancies or uncertainties have been adequately clarified by the theory that angina pectoris is the result of myocardial anoxia due to a transient acute coronary insufficiency.[69] That only a small percentage of cases of coronary sclerosis are associated with angina pectoris[122] is due to the fact that significant interference with the blood supply to an area of myocardium (i. e., coronary insufficiency) can occur only when the vascular lumen is narrowed extremely or entirely obstructed. Mann and associates[90] demonstrated that the internal diameter of a vessel could be decreased to one-half its original diameter over a distance of 8 to 10 mm. without reducing its blood flow significantly. Even with complete obstruction of a vessel, its area of supply may receive an adequate amount of blood through collateral anastomosing vessels, provided that the obstruction became complete only after a long interval of slowly progressive arterial narrowing. This is indicated by the studies of Blumgart, Schlesinger and Davis[7] who demonstrated that angina pectoris occurred as a rule after two, and exceptionally after one, major coronary artery was occluded and the remaining major branches were severely narrowed. Blumgart, Schlesinger and Zoll[8] demonstrated that in cases of old coronary occlusion without a history of angina pectoris there was an average of 1.4 occlusions per heart, whereas in cases of old coronary occlusion with a history

of angina pectoris, there was an average of 3.5 occlusions per heart. These findings also support the probability that the onset of the first paroxysm of angina pectoris is due to an acute coronary occlusion without infarction, rather than to progressive narrowing. Otherwise it is difficult to understand why a man who daily takes the same walk to his bus or train suddenly finds himself incapable of doing so without pain. Frequently there is no pain until the occurrence of a clinical attack of acute coronary occlusion with infarction; angina pectoris appears following convalescence and resumption of activity.

The opposite circumstance, that angina pectoris was sometimes observed in the absence of significant coronary artery lesions, may be accounted for in several ways. Recent improvements in the postmortem study of the coronary arteries have demonstrated that former investigators often overlooked severe coronary artery disease,[71] especially coronary artery occlusions. Thus my own investigations with the late Dr. Louis Gross and those of my associates,[58] like those of Saphir et al.,[122] and more recently of Blumgart et al.,[7, 8] have shown that multiple coronary occlusions are much more common than formerly believed and that the right coronary artery and left circumflex artery are occluded almost as often as the left anterior descending, whereas older observers usually discovered occlusions only in the latter. Sometimes, also, in coronary vessels which appeared patent throughout their course extreme narrowing or obliteration of the ostia due to syphilitic aortitis was formerly overlooked. Furthermore, it is now recognized that coronary insufficiency and angina pectoris may occur in the presence of normal coronary arteries, as a result of other cardiovascular or valvular diseases which disturb circulatory dynamics so as to diminish the coronary blood flow or increase the myocardial requirement. These other causative diseases, such as aortic stenosis, have been listed above.

Theories of Angina Pectoris

Evidence for the Theory of Myocardial Anoxia *(Secondary to Coronary Insufficiency).* 1. The pathologic data presented above are the strongest evidence for the belief that coronary insufficiency and resulting myocardial anoxia account for angina pectoris. In most instances there is an actual mechanical interference with a major portion of the blood supply to the myocardium. In the remaining cases there are pathologic abnormalities in the valves, the heart or the circulation which lead to a diminution in coronary blood flow and an augmentation of myocardial blood demand or an impoverishment of the oxygen content of the blood.

2. That obstruction of the coronary circulation may cause pain was indicated by the experimental observations of Sutton and Lueth[134] on unanesthetized dogs. These authors caused the animals to become restless and tachypneic and to behave as if they were in pain whenever they temporarily ligated a large coronary artery. Furthermore, temporary clamping of a coronary artery in experimental animals results in reversible electrocardiographic changes[34, 149] resembling those seen during attacks of angina pectoris in humans.

3. Additional support is found in the similarity in character, location and distribution of the pain in acute coronary occlusion and that of angina pectoris. That the pain of the former is due to myocardial anoxia is readily accepted because of the pathologic finding of myocardial necrosis. It is therefore likely

that myocardial anoxia of less intense degree and briefer duration may be invoked to explain the similar but more transient pain of angina pectoris. The observation of Büchner[15] that careful study will demonstrate focal necrosis of the myocardium in patients who had suffered from attacks of angina pectoris just before death indicates that the myocardial anoxia of angina pectoris may produce anatomic as well as functional alterations.

4. More direct evidence that the pain of angina pectoris is due to myocardial anoxia was supplied by the experiments of Rothschild and Kissin[120] and of Dietrich and Schwiegk.[27] These observers induced generalized anoxemia in patients who presented a history of angina pectoris or other evidence of coronary disease, by having them rebreathe low oxygen mixtures or by placing them in a chamber with low oxygen tension. In a high percentage of these cases, an attack of angina pectoris was induced during the experiment, and electrocardiographic alterations similar to those which occur when patients suffer spontaneous attacks of angina pectoris were observed. With the administration of normal concentrations of oxygen, the pain disappeared and the electrocardiogram reverted to its previous appearance.

5. Cases in which severe anemia either by itself or in association with underlying coronary disease provokes attacks of angina pectoris also support the theory that the latter is due to myocardial anoxia. For the essential abnormality in anemia is reduction in the oxygen-carrying power of the blood. In at least some of these cases it has been shown that when the anemia is relieved by transfusion the attacks of pain cease promptly.[106, 60] It has also been shown that both in experimental and clinical carbon monoxide poisoning[3] in which the oxygen combination with hemoglobin is replaced by carbon monoxide, electrocardiographic changes and myocardial necrosis occur similar to those observed in human cases of angina pectoris.[22] Similarly in animals and humans exposed to high altitudes (above 5000 meters) corresponding to an oxygen saturation of the atmosphere of 80 per cent or less, electrocardiographic changes occur which are similar to those seen with spontaneous or induced attacks of angina pectoris. These observations indicate that it is the deficiency in oxygen which is the essential cause of angina pectoris.

6. The pathogenesis of the pain of intermittent claudication of the lower extremities has been used by analogy to support the anoxic theory of angina pectoris. In experiments simulating intermittent claudication, MacWilliam and Webster,[88] and Lewis, Pickering and Rothschild,[83] showed that interruption of the arterial flow in the arm gave no pain if the arm was at rest. However, if the arterial flow was reduced, and the hand and forearm exercised, pain occurred and was located not in the course of the artery but in the working muscle, distal to the obstruction. The observations were interpreted to indicate that the oxygen requirement of the *resting* muscle was satisfied even when the arterial flow was reduced, but that when the muscle was exercised the greater oxygen need of the active muscle could not be supplied, with consequent appearance of pain. By analogy, a patient with diminished coronary blood flow may have no pain at rest, but suffers an attack of angina pectoris when the work of the heart is increased during bodily exertion.

7. The theory of myocardial anoxia is compatible with the frequency of sudden death in patients with angina pectoris, for it is generally believed that sudden death is usually due to ventricular fibrillation[87] and the latter is especially favored by an oxygen deficiency of the myocardium.[126]

Other Theories of the Pathogenesis of Angina Pectoris. *Aortic Theory.* The occurrence of angina pectoris in cases without significant lesions in the coronary arteries led some of the older observers to seek a noncoronary explanation for the origin of angina pectoris. The aortic theory, advocated most strongly by Sir Clifford Albutt[1] and by Wenckebach,[140] presumed that angina pectoris was caused by disease at the root of the aorta. The pain was thought to result from dilatation of the aortic root and stretching of the nerve fibers in the aortic adventitia and periadventitial tissue. This theory was supported by the pathologic observation of arteriosclerotic or syphilitic lesions in the aorta in almost all of the cases of angina pectoris including those in which coronary lesions were absent.

However, the aortic theory of angina pectoris has been abandoned because: (1) Angina pectoris occurs in only a small proportion of cases in which there is aortic arteriosclerosis or syphilitic aortitis. (2) In cases of rheumatic aortic insufficiency and of calcific aortic stenosis with angina pectoris, there are often no significant abnormalities of the aorta. (3) It does not account for the characteristic occurrence of sudden death. (4) It does not explain many of the clinical and electrocardiographic features of angina pectoris as well as the theory of myocardial anoxia.

Theory of Coronary Spasm. Those who reject the aortic theory of angina pectoris and accept that of coronary insufficiency and myocardial anoxia are divided as to the mechanism by which the coronary insufficiency and angina pectoris are produced. Most proponents of the coronary theory believe that the circulatory deficiency arises chiefly as a result of mechanical reduction in coronary flow due to occlusion or extreme narrowing of the vessels, or as a consequence of cardiac lesions, notably aortic valvular disease, which may cause disturbances in the dynamics of the coronary circulation with a reduction in blood flow. The actual paroxysm occurs when exercise, emotion, digestion or the like rapidly increase the myocardial needs for oxygen, which the deficient coronary circulation cannot supply.

A second group of proponents of the coronary theory believe that coronary arterial spasm is responsible for the actual attack of angina pectoris, whether or not there is underlying organic disease of the vessels.[72, 40, 73] The hypothesis of coronary spasm was invoked particularly to explain cases of angina pectoris and sudden death in which significant coronary lesions were not found at necropsy.[74] It also appeared to account for attacks of angina pectoris occurring at rest, especially those unassociated with tachycardia or an elevation in blood pressure, or without any other apparent reason for diminished coronary blood flow or increased cardiac work. Coronary spasm could also explain the sudden occurrence and disappearance of the paroxysm, its reversible nature and its relief by vasodilator drugs such as the nitrites.

Except for such rare unexplained occurrences as the complete disappearance of the radial pulse during an attack of angina pectoris,[89] there is no significant positive evidence for the theory of coronary spasm, since such spasm has never been observed. Experimental evidence that distention of the esophagus or stomach may cause reflex vagal coronary vasoconstriction has been mentioned. Prolonged vagal stimulation or administration of acetylcholine was reported to have produced severe coronary artery degeneration and thrombosis.[33] These observations have been used to support a concept of coronary artery spasm due to vagal vasoconstriction. Various specific objections to this

hypothesis have been raised by Goldenberg and Rothberger[46] on the basis of their experimental studies.

Site of Origin and Cause of Pain

It is most likely that the pain of angina pectoris arises in the heart muscle, although the aorta and the coronary arteries have also been implicated as the site of its origin. The aortic adventitia is rich in nerve endings which, it is assumed, transmit painful sensations when the aorta is diseased and distended by increased intravascular tension such as may accompany exercise. However, Sutton and Lueth[134] were unable to produce pain in unanaesthetized dogs by stretching of the normal or inflamed aorta. Furthermore, the pathologic data presented above indicate that aortic disease, except when it occludes the coronary ostia, is not the underlying cause of angina pectoris.

Sutton and Lueth[134] produced pain, as manifested by restlessness and distress, in unanaesthetized dogs by temporary, partial or complete constriction of a large coronary artery. The pain was associated with rigidity and limping of the left foreleg, signs which were interpreted as corresponding to the referred pain and muscle spasm in the left arm of humans with angina pectoris. While Sutton and Lueth concluded that the pain resulted from a diminished coronary flow to the myocardium, other observers have suggested that the cause of pain following experimental coronary narrowing or occlusion was a direct stimulation of the nerve plexus surrounding the artery,[68] or a distention of the coronary artery proximal to the obstruction associated with increased pressure in that segment.[47] But Wiggers and Cotton[144] demonstrated that occlusion had no effect on the proximal coronary pressure, and Sutton and Lueth[134] excluded coronary distention or pressure on the pericoronary nerves by producing pain in their dogs when the mouth of a coronary artery was plugged by a brass rod with a knob at its end. These observations, as well as the similar experimental observations of White, Garry and Atkins[141] and of Shambaugh,[125] and the data presented above to support the theory of myocardial anoxia lead to the conclusion that the pain associated with angina pectoris arises in the heart muscle and not in the aorta or coronary arteries.

The exact *stimulus* which gives rise to pain is uncertain, but it is most generally believed that it is a chemical one related directly or indirectly to the lack of oxygen in the muscle tissue. However, it is still undetermined whether the oxygen lack directly or whether the accumulation of metabolic products which are incompletely washed away by the coronary blood actually provides the stimulus for pain.[88, 83, 70] In summarizing the various experimental and clinical observations on the pain of angina pectoris, Katz[67] concluded that the stimulus responsible for pain is one or more acid metabolities such as lactic, pyruvic or phosphoric acid, or some nonacid metabolite such as histamine, phosphocreatine, adenosine or potassium,[48] which is formed during cardiac contraction and accumulates in excessive amounts only when there is a relative oxygen deficiency.

Nervous Pathway of Pain in Angina Pectoris

Recent anatomic and experimental studies and the effects of nerve block or excision in humans have added greatly to our still incomplete knowledge of the pathway by which pain is conducted from the heart. A detailed discussion is

presented in the monographs of White and Smithwick,[142] and of Miller.[92] The stimulus for the pain arises in the heart muscle itself, but the pain fibers are located in a rich plexus in the adventitia of the coronary arteries and in the periarterial subepicardial tissue.[55] Sutton and Lueth[134] and Katz, Mayne and Weinstein[68] demonstrated that after destruction of the pericoronary nerves by excision or painting with alcohol, pain no longer appeared following experimental coronary occlusion in dogs.

The pain impulses apparently are conducted only through the sympathetic nerves, although afferent as well as motor fibers are also present in the vagus. After reaching the periarterial nerves, the pain impulses traverse the superficial and deep cardiac plexuses and then course through thoracic cardiac nerves[61] to the upper four or five thoracic (paravertebral) sympathetic ganglia. Other pain fibers from the cardiac plexuses extend in the superior, middle and lower cervical cardiac nerves to the corresponding cervical sympathetic ganglia and then descend again to the upper four or five thoracic sympathetic ganglia.

Having thus reached the upper thoracic sympathetic ganglia directly or indirectly, the pain impulses enter the cord by way of the white rami communicantes which join these ganglia to the upper four or five thoracic spinal nerves. As a practical basis for understanding the rationale of nerve block in the treatment of severe, protracted angina pectoris, it should be recognized that all the nerve impulses arising in the heart and traversing the sympathetic nerves eventually converge in the upper four or five thoracic sympathetic ganglia and spinal thoracic nerves. White, Garry and Atkins[141] demonstrated that the pain caused by constriction of the anterior descending coronary artery in dogs could still be elicited after both vagi in the neck were cut or after the stellate ganglia and inferior portion of the sympathetic chains were resected. However, coronary constriction failed to result in pain, following resection of the stellate and upper four pairs of thoracic sympathetic ganglia, or resection of the upper five pairs of the thoracic posterior spinal roots. These findings are in harmony with the observation that anesthesia of the above-mentioned ganglia effectively relieves pain in humans with angina pectoris.

The Physiologic Basis for the Perception and Radiation of Anginal Pain

The pain arising in the heart eventually reaches the thalamic regions of the brain, probably ascending in the spinothalamic tract of the cord. It is believed that since the pain fibers from the heart join the spinal nerves before entering the cord, the same segments of the cord (D1–D5) receive visceral pain sensations from the heart and somatic pain sensations from the corresponding areas of the body surface known as dermatomes. According to the Mackenzie[86] theory of referred pain, the pain impulses arising in internal organs are not perceived as originating in these organs, but appear to arrive from the corresponding peripheral dermatomes, which send afferent nerves to the same segments of the cord as the internal organ.[86, 50] With respect to the heart, the corresponding surface area, chiefly D1–D4, includes the precordium, the medial half of the anterior surface of the arm, the forearm and fifth finger. However some of the pain arising in the heart may not be referred but may reach the thalamus directly and be perceived as arising in the heart. This may account for the primary oppressive discomfort, localized to the retrosternal region.

The reason for the variations in the occurrence and radiation of the pain in

patients with apparently similar coronary lesions is still unclear. Undoubtedly these variations are due in part to individual differences in sensitivity to pain in general. By noting the response of individuals to pressure over the styloid process, Libman[84] has classified human subjects into two general groups, the hyposensitive and the sensitive. Sensitive subjects usually present the classic symptoms of any given painful disease, including the pain with typical radiations. Hyposensitive subjects are apt not to have pain, or to have pain in atypical radiations or to have substitution symptoms referable to the autonomic nervous system, a number of which are brought about by reflex mechanisms. Thus hyposensitive subjects with coronary disease are likely to suffer burning, coldness, a sense of pressure or constriction of the chest or a feeling of swelling of the arms or forearms instead of pain; pain, if present, may be contralateral or have contralateral or inverse radiations. Libman believed these differences may be due to a more direct transmission of painful impulses to the central nervous system in the sensitive individual; in hyposensitive individuals the impulses appear to be delayed in the autonomic nervous system.

The pain of angina pectoris which arises in the heart differs in quality from pains of somatic origin which are localized to similar areas of the chest wall and arms. Pain is believed to be transmitted by slow conducting medullated (B group) and nonmedullated (C group) fibers.[52] Differences in quality of pain may be determined by various possible combinations of B and C fibers which are simultaneously excited, the duller and more prolonged visceral pain representing a greater preponderance of excited nonmedullated C fibers. The pain fibers running directly from the heart to the central nervous system may produce a special modality of pain, which differs from that perceived through somatic afferent radiations.

Some of the distinctive features of the pain of angina pectoris and of associated phenomena are due to vagal and sympathetic efferent and somatic motor reflexes which are initiated by the afferent pain impulses. Reflex muscular spasm may account at least in part for the shoulder pain and weakness of the upper extremities as well as for the sense of compression and fixation of the chest wall. The sense of strangling may in at least some cases be due to reflex spasm of the pharyngeal muscles. Sweating and other vasomotor disturbances and gastrointestinal symptoms associated with angina pectoris may be due to vagal and sympathetic reflexes.

Angina Pectoris and Congestive Heart Failure

There is no intimate relationship between angina pectoris and congestive heart failure. In fact it is a common observation that patients with angina pectoris usually lose their pain when congestive heart failure develops. Usually the manifestations of congestive heart failure, especially dyspnea, by considerably curtailing the patient's activities, eliminate the chief precipitating factor of angina pectoris, namely physical exertion. In other instances, the onset of congestive heart failure follows an acute myocardial infarction. After subsidence of the acute episode there may be no further angina pectoris. This may be due to complete destruction of the anoxic area of myocardium which was previously responsible for pain; the development of heart failure is merely coincidental. This mechanism is often unrecognized because the infarction may be silent as regards pain, fever, etc., and the appearance of congestive heart failure may be its only manifestation. The disappearance of attacks of angina

pectoris with the development of permanent auricular fibrillation is probably also determined by the frequently associated congestive heart failure. Despite the usual incompatibility of angina pectoris and heart failure, it is worthy of note that angina pectoris may sometimes persist or become intensified after the onset of heart failure. In such circumstances it may be assumed that the factors causing heart failure have simultaneously so increased the degree of coronary insufficiency that pain occurs in spite of diminished activity.

So-called angina pectoris has been observed during attacks of paroxysmal nocturnal dyspnea (cardiac asthma) due to left ventricular failure.[100] Some of these attacks of pain represent an acute coronary occlusion. In other instances, there is precordial discomfort due to acute dyspnea, which however may not properly be termed angina pectoris. Aside from these exceptions there are true instances of angina pectoris occurring at night in patients at rest with or without concomitant paroxysmal dyspnea. Acute left ventricular dilatation, elevation of blood pressure, tachycardia and consequent increased work of the heart have all been invoked to explain the occurrence of this angina pectoris, so-called angina decubitus. But the actual cause remains obscure. It does appear that while chronic left- and right-sided congestive heart failure tend to dispel or diminish attacks of angina pectoris, acute left ventricular failure may be associated with or responsible for such attacks.

Angina Pectoris and Acute Coronary Occlusion. *See page 367.*

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18

ANGINA PECTORIS

Diagnosis, Differential Diagnosis, Prognosis and Treatment

DIAGNOSIS

The identification of a pain or distress in the chest as angina pectoris does not constitute a complete diagnosis, for angina pectoris is a symptom-complex and not a disease. However, the recognition of angina pectoris is an important diagnostic step, since its presence denotes some serious underlying cardiac ailment, usually coronary artery disease.

The Clinical History

The diagnosis of angina pectoris depends primarily on the clinical history and not on objective findings. However, the presence of an underlying cardiac disease or a positive response to tests disclosing coronary insufficiency supports the diagnosis of angina pectoris.

The essential diagnostic features of angina pectoris are: (1) the paroxysmal occurrence of the pain, (2) its brief duration, (3) its characteristic location, radiation and quality, (4) its precipitation by effort and relief by rest, and (5) its relief by nitrites.

These points require brief annotation: (1) Sometimes there is a dull persistent pain or ache between the paroxysms, varying in intensity, but there must also be definite paroxysms to warrant the diagnosis of angina pectoris.

(2) Attacks of angina pectoris usually last less than five minutes and rarely exceed fifteen minutes. Apparent paroxysms of angina pectoris of longer duration probably denote an acute coronary occlusion or impending myocardial infarction, even when there are no significant electrocardiographic abnormalities.

(3) The location of the pain over the sternum or precordium is characteristic but not specific for angina pectoris. Radiation to the left shoulder, arm and wrist is also suggestive of angina pectoris, but not essential for the diagnosis. The strangling, constricting or compressing quality of the pain and the frequent association of angor animi are valuable diagnostic features. Dull or sticking pains and pain in the region of the cardiac apex, in the lower part of the left axilla or below the left breast are rarely manifestations of angina pectoris.

(4) The diagnosis of angina pectoris is equivocal if there is no history of

the precipitation of the pain by effort and its relief by rest. But sometimes no such history is elicited because the patient has avoided all but the mildest activity or because he has not walked far enough or rapidly enough to induce pain. He should be asked specifically: "Do you have pain on walking rapidly, on hurrying or on walking uphill? Can you continue the same pace once the pain begins? Is it relieved by slowing your pace or by stopping?" When the pain is induced by walking, it has an arresting quality which compels the patient to stop or sharply reduce his speed. The pain of angina pectoris occurs frequently with excitement, anger or other emotional states, and this relationship should not be interpreted as indicating that the pain is psychogenic, provided there are other occasions when the pain is produced in typical fashion by effort and relieved promptly by rest. Pain induced *only* by emotional states is not usually due to angina pectoris. It may be necessary to test the effect of effort and rest in order to be certain of their relationship to the pain. Sternal or precordial pain which is induced by fatigue or after working long, but which is not promptly relieved by rest, should not be interpreted as a manifestation of angina pectoris.

(5) The response to nitrites, especially nitroglycerin or amyl nitrite, is often helpful in diagnosis. The diagnosis of angina pectoris is supported if the relief of the pain, pressure or "indigestion" is definite, prompt and unquestioned by the patient. I have, however, observed patients suffering from pain in the chest, which was relieved by nitroglycerin, but which was later proved to be unrelated to cardiac or coronary disease.

In addition to the above the sex of the patient is of diagnostic value. In the absence of persistent diastolic hypertension or diabetes mellitus, the diagnosis of angina pectoris should be made with reservation in a woman unless the clinical features are typical and there is evidence of an underlying disease capable of producing coronary insufficiency.

Objective Evidences of Cardiac Disease

When the essential symptomatic criteria are satisfied, the diagnosis of angina pectoris may be made with certainty even in the absence of objective findings. In doubtful cases of pain in the chest, however, a suspected diagnosis of angina pectoris may be supported by finding hypertension, significant cardiac enlargement, aortic valvular disease or such electrocardiographic abnormalities as frequently accompany severe coronary artery disease (see p. 348). Occasionally it is possible to take an electrocardiogram during an attack of pain; the presence of a transient ST depression and lowering or inversion of the T waves with a return to normal soon after the pain subsides strongly suggest that the pain is a manifestation of angina pectoris. Occasionally RS-T elevations have been observed during an attack of angina pectoris resembling those commonly seen with acute myocardial infarction.[94, 69] However, such changes may occur only when there were persistent electrocardiographic abnormalities due to previous myocardial infarction.

Tests of Coronary Reserve and Coronary Insufficiency

It has been mentioned that there is a margin of safety whereby a diminution in the coronary blood flow or an increase in the myocardial blood requirements may occur without resulting in coronary insufficiency or angina pectoris. This margin represents the coronary reserve. In subjects with a seriously impaired

coronary circulation, the coronary reserve is already so diminished that any factor tending to cause anoxemia is likely to result in myocardial anoxia sufficient to produce angina pectoris or electrocardiographic changes. This principle has been utilized as the basis of tests for coronary insufficiency. The demonstration of a diminished coronary reserve by such tests is interpreted to indicate that retrosternal or precordial pain in a given patient probably represents angina pectoris. Among the factors utilized to induce coronary insufficiency in patients with diminished coronary reserve are generalized anoxemia, exercise, and less frequently epinephrine, pituitrin or exposure to cold. These tests are of value in only a very small percentage of cases of angina pectoris; an accurate diagnosis is almost always possible on the basis of the clinical history supplemented by routine examination. However, objective tests are useful

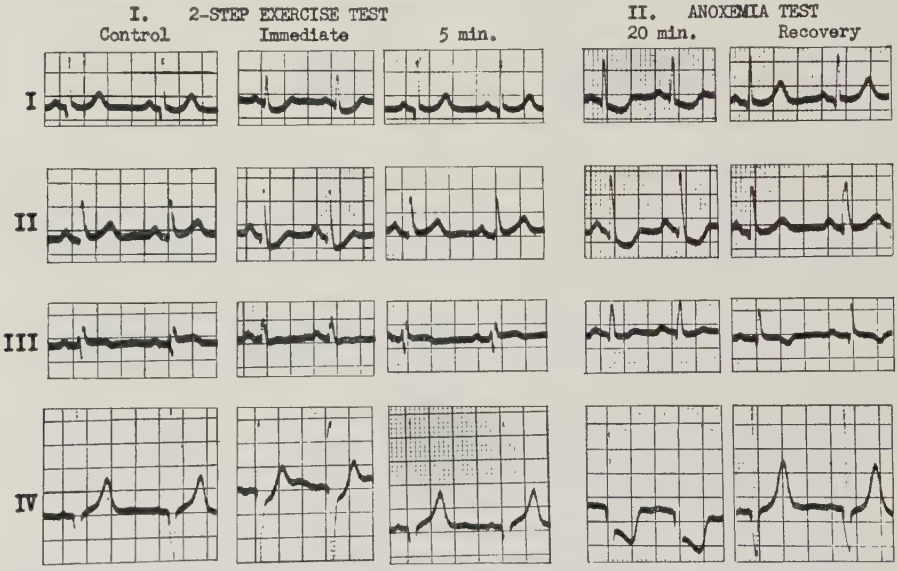


Fig. 48. Exercise and anoxemia test in coronary artery disease on same patient. Positive test for coronary insufficiency with both tests. Pronounced S-T segment depressions.

in problems of insurance and medicolegal practice because of the possibility that a history of angina pectoris may be fabricated.

Anoxemia Test (Hypoxemia Test). Generalized anoxemia is induced by having the subject breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes, unless cardiac pain is experienced before that interval.[45] The subject is permitted to breathe 100 per cent oxygen for one minute immediately after concluding the test or if there are any unpleasant reactions. Electrocardiograms are taken just before the test and at five-minute intervals until the electrocardiogram has returned to its control form. The test is termed positive (Fig. 48) and considered indicative of coronary insufficiency or diminished coronary reserve if pain occurs during the procedure or if the following electrocardiographic abnormalities are noted: (1) The sum of the RS-T deviations in leads I, II, III and IVF exceeds by 3 mm. or more that of the control. (2) There is partial or complete reversal of the direction of the T wave in lead I, accompanied by an RS-T deviation of 1 mm. or more in this lead. (3) There is a complete reversal of the T wave in lead

IVF regardless of any associated RS-T deviation in this lead. Burchell and his associates[13] found that the precordial leads were more informative than the standard leads and could be used exclusively if desired. The diagnostic changes in lead CR_5 were: pronounced depression (more than 2.0 mm.) of the RS-T segment or frank reversal of the T wave. In cases of old anterior apical infarction, there may be an elevation of the R-T segment following generalized hypoxemia. Characteristic chest pain during the test is probably due to coronary insufficiency and, as a rule, is accompanied by the diagnostic electrocardiographic changes, but frequently these electrocardiographic abnormalities appear without pain. The S-T depressions appear to denote that myocardial anoxia is most pronounced in the subendocardial layer and that this is electrically positive relative to the subepicardial layer. A negative test does not exclude angina pectoris or coronary insufficiency.

Patterson, Clark and Levy[65] found the test to be electrocardiographically positive in 49 per cent of 157 cases of coronary sclerosis. In an additional 20 per cent the occurrence of pain without electrocardiographic changes also offered presumptive evidence of coronary insufficiency. Compared to this total of 69 per cent positives in patients with coronary disease, there was no instance of pain or a positive electrocardiographic test in 136 normal subjects. Other observers have obtained positive tests in 30 to 55 per cent of cases with probable or definite clinical coronary disease, in 15 to 20 per cent of suspected cases and in 0 to 2.7 per cent of normals or "slightly suspected" cases.[8] Biörck[9] observed a positive anoxemia test in 9 patients with cardiac neurosis without organic heart disease. There was a negative response when 0.5 mg. ergotamine tartrate was given intramuscularly or subcutaneously twenty minutes before the anoxemia. Dihydroergocornine (0.5 mg.) is similarly used and is preferable.

Although occasional unpleasant and even serious reactions have been observed during the hypoxemia test[87] (dizziness, headache, drowsiness, nausea, cyanosis, anxiety, numbness, hysteria, vasovagal syncope, air hunger, chest pain, arrhythmia, convulsions and pulmonary edema), the serious ones have become rare as technic has improved and been standardized, and discretion used in the choice of subjects. Burchell and his associates[13] have performed 730 hypoxemia tests without a fatality. Among the contraindications to the anoxemia test are: age past sixty, obvious cardiac enlargement, definite previous myocardial infarction, chronic pulmonary disease, severe anemia, pregnancy, acute illness, advanced debility. Because of the risk of reactions, however small, the need for technical equipment and special skill in the choice of patient and in the interpretation of findings, the anoxemia test is not yet suitable for general use.

Exercise Test of Coronary Reserve. Exercise strains the coronary reserve by increasing the myocardial need for blood. A standardized amount of exercise is performed (e. g., the two-step test of Master and Oppenheimer[53] or that of Riseman and Stern[72]). In patients with a diminished coronary reserve, the exercise may produce pain or distinctive electrocardiographic changes.[85, 52] A positive test is associated with the following changes:[85]

(a) ST segment depression or elevation of 1 mm. or more in lead I, of 1.5 mm. or more in lead II, of 1.5 mm. or more in lead III and 2 mm. or more in lead IV;

(b) the conversion of an upright to a diphasic or inverted T wave in lead I, II or IV;

(c) the development of bundle branch block.

According to Master et al.[52] the electrocardiographic abnormalities are due to a lack of oxygen supply to the heart because identical changes were reproduced in the same subjects by having them breathe oxygen in low concentration (10 per cent). Twiss and Sokolow[85] reported that cardiac pain developed during the test in 45 of 66 patients known to have angina pectoris. The above-mentioned significant electrocardiographic abnormalities appeared in two thirds of those who experienced pain during the test and in 56 per cent of the total number of patients with angina pectoris regardless of the development or absence of pain. Obviously a normal response does not exclude the presence of angina pectoris. False positive tests were obtained by Master and associates[52] in neurocirculatory asthenia, pulmonary disease and upper respiratory infections.

The exercise test has a number of advantages over the anoxemia test. Exercise is the factor which most characteristically induces clinical attacks of angina pectoris; absolute anoxemia is rarely responsible. The test is simpler to perform and requires less technical accuracy and equipment. Unlike anoxemia, exercise does not produce significant impairment of the central nervous system. Although the exercise test has potential danger for the patient with serious coronary disease, it is rarely harmful; in actual practice there are none of the unpleasant reactions sometimes observed during the anoxemia test. On the other hand the anoxemia test permits better control and standardization of conditions and can be performed on patients who are not ambulant. The results obtained with exercise and anoxemia tests on the same patient are essentially similar.[21, 52, 8, 81] However, disagreement as to the criteria for a positive test and differences in technic among those who administer the exercise test make comparisons difficult.[52, 73, 8]

Epinephrine and Other Tests of Coronary Reserve. The subcutaneous injection of 1 cc. of 1:1000 dilution of epinephrine has been used as a diagnostic test of angina pectoris.[42] In patients with angina pectoris this drug was said to reproduce an attack and to cause electrocardiographic changes, neither of which was observed in normal controls. However, the danger of severe reactions, including the precipitation of myocardial infarction, and the variable effects of the drug have prevented the adoption of this test.

Pitressin. The coronary constrictor effect of pitressin has led to its trial as an objective test of coronary insufficiency. Positive results in 8 of 12 patients with angina pectoris were observed following the intravenous administration of 0.75 cc. (15 pressor units) of pituitrin or the intramuscular injection of 2 cc.[74] A positive test is documented by the development of flat, diphasic or inverted T waves in leads I, II or IVF and S-T depressions in leads I, II, III and IV totaling 3 mm. or more.

DIFFERENTIAL DIAGNOSIS

A great variety of conditions associated with chest pain are sometimes mentioned as requiring differentiation from angina pectoris. However, when the distinctive clinical character of angina pectoris is clearly understood, its confusion with other diseases causing pain in the chest and upper extremity should be rare. Almost always the typical clinical history suffices to make the differentiation. If not, a consideration of the age and sex of the patient, the presence or absence of hypertension and diabetes, and objective physical,

roentgenologic and electrocardiographic signs of heart disease usually clarify a doubtful case. The use of the exercise or anoxemia tests discussed above may prove diagnostically helpful. Finally, roentgenologic investigation of the lungs and mediastinum, the spine, ribs, shoulder joints, esophagus, gastrointestinal and biliary tracts may be necessary to disclose the organic basis for pain in the chest, shoulder or arm. But it is essential, even when such lesions have been uncovered, to review the clinical history carefully to determine whether angina pectoris is present in addition to an associated noncardiac disease.

Diseases Simulating Angina Pectoris. Among the conditions which cause pain in the chest, sometimes confused with angina pectoris, are: (1) Psychoneurosis (conversion neurosis). (2) Neurocirculatory asthenia. (3) Functional disturbances of the gastrointestinal tract with gaseous distention. (4) Costochondritis, a slipping rib, neuralgia, fibrositis or myalgia of the left anterior chest wall, or injury to the pectoralis minor tendon. (5) Peptic gastric or duodenal ulcer. (6) Cholelithiasis and chronic cholecystitis. (7) Esophagospasm. (8) Diaphragmatic or paraesophageal hernia. (9) Radiculitis secondary to cervical dorsal spondylitis. (10) Subacromial bursitis or periarthritis of the left shoulder. (11) Cervical rib. (12) Scalenus anterior syndrome. (13) Metastatic cervical lymph nodes compressing the brachial plexus. (14) Pleurisy. (15) Pericarditis. (16) Aneurysm of the aorta. (17) Carcinoma or suppuration of the lung or mediastinal neoplasm. (18) Diaphragmatic flutter.[14] (19) Carotid sinus syndrome.[27]

The differentiation of angina pectoris from acute myocardial infarction will receive special discussion (see p. 470).

Relation of the Pain to Exertion. Pain in the above conditions is chiefly distinguished from angina pectoris by being unrelated to general bodily exertion, especially walking rapidly or uphill. The pain secondary to subacromial bursitis, arthritis of the shoulder and spine or local disease of the chest wall may be precipitated by exercise of the local areas but not by general bodily effort. Active or passive movement of the left arm or cervical and thoracic spine through its complete range of motion or deep inspiration, coughing or sneezing may reproduce the pain and disclose its noncardiac origin; immobilization of the affected part may eliminate or diminish the pain even during general bodily exertion. The occurrence of the pain with emotional states is not decisive, being as common with neuroses and functional disturbances of the gastrointestinal tract as with angina pectoris.

Character and Location of the Pain. The character and location of nonanginal chest pain often aid in differentiation from angina pectoris. A dull ache in the precordial region or above and to the left of the heart is common in neurotic persons, or as a result of pectoral myalgia or neuralgia. A dull ache or sharp, sticking or stabbing pain in the region of the cardiac apex or in the left breast also occurs frequently in neurotic subjects. In addition, there is often a complaint of excessive fatigability, palpitation, diffuse pains in different parts of the body and difficulty in taking a deep breath (characterized objectively by sighing respiration). The pain often radiates around the ribs and to the left subscapular region. In addition to the difference in site and character of this pain, it is usually indefinite in onset as compared with the paroxysmal nature of the attacks in angina pectoris. The pain occurs at rest as well as with effort, and especially when the patient is fatigued. There is often an hyperesthesia in the painful area, usually in the segmental distribution

of D4 and D5 rather than of C8 and D1 as in angina pectoris.[3] A similar type of pain occurs in subjects with indigestion, especially in middle-aged obese men and women. This form of pain, often in association with other diffuse pains, variously located in the chest and abdomen, results from gastrointestinal gaseous distention.

Dull and sticking precordial pain or discomfort, usually associated with palpitation, frequently results from paroxysmal tachycardias and runs of premature beats. A sense of anxiety or even a fear of impending death may lead to a superficial resemblance to angina pectoris. A careful history and examination readily disclose the relation of the pain to the arrhythmia.

The pain of gastric and duodenal ulcer is usually situated in the epigastrium and lower sternal region; it has a burning or boring quality, is unrelated to effort and occurs usually one to four hours postprandially, whereas angina pectoris is apt to occur more promptly after meals and usually only with postprandial exertion. Ulcer pain ordinarily is relieved rapidly by alkalis and milk.

The pain due to pleurisy or pericarditis is unlikely to be confused with angina pectoris because of associated clinical symptoms, the presence of fever and other objective evidences of infection and local disease, the sharp nature of the pain and its frequent occurrence with deep inspiration.

Expanding or dissecting aneurysms produce a more constant crushing type of pain than is associated with angina pectoris.

Occasionally I have seen cases of carcinoma or suppuration of the left upper lobe of the lung with chest pain interpreted as angina pectoris. The pain is usually more intense and persistent than that of angina pectoris, although it may be located in the precordium and may radiate to the left upper extremity.

Differentiation of Local Lesions of the Chest Wall by Physical Examination. Physical examination often reveals the local origin of pectoral pain. Careful palpation of the ribs may disclose a fracture, due perhaps to a metastatic lesion or involvement by a myeloma. Examination of the costochondral junctions, especially on the left side, may demonstrate that the pain is due to an arthritis of one or more of these joints, or to a fibrositis. This occurs more commonly than is generally recognized. Local infiltration of 1 per cent procaine often relieves the pain but similar relief has been reported in cases of angina pectoris. Occasionally digital manipulation may demonstrate that the slipping of one rib under another is the cause of precordial pain. The pain is usually prevented by strapping the affected chest wall. A slipping rib cartilage[36] may also cause chest pain which has been confused with angina pectoris. Usually the cartilages of the eighth, ninth or tenth rib are involved, having been dislocated or displaced by fracture. The pain can be reproduced by digital examination with the patient supine, his knees flexed. Manipulation of the movable rib cartilage causes pain and an audible click. The pain may be cured by strapping or resection of the affected cartilage. Strain of the left pectoralis minor muscle was described as a common cause of chest pain in soldiers.[54]

Roentgenologic Differentiation of Biliary, Gastrointestinal, Aortic, Pulmonary and Skeletal Disease. The underlying cause of many types of chest pain is often determined or proved by roentgenologic examination. This applies to cholelithiasis, peptic ulcer, diaphragmatic or esophageal hernia, aortic aneurysm, pleuropulmonary disease, subacromial bursitis, arthritis of the left shoulder or cervicodorsal spine, or destructive lesions of the ribs. Roentgenologic examination of the chest including its bony cage, of the cervical spine and

left shoulder joint, and of the esophagus, stomach, duodenum and biliary tract are often essential to the accurate interpretation of pain simulating angina pectoris.

In recent years cholelithiasis and chronic cholecystitis have been particularly stressed as causes of pain simulating angina pectoris. The pain due to disease of the biliary tract may radiate to the epigastrium, sternal region or even the precordium, but the characteristic quality of anginal pain, its relation to effort and other features of angina pectoris, are not simulated exactly. Disease of the biliary tract may also favor the occurrence of anginal pain in one who has angina pectoris due to coronary sclerosis. But if the classic clinical features of angina pectoris are present, they must be attributed to coronary, aortic or other causative underlying cardiovascular disease, whether or not cholelithiasis and cholecystitis are also present. The combination of coronary disease and disease of the biliary tract is common. Thus the roentgenologic demonstration of gallstones and a nonfunctioning gallbladder does not exclude the coexistence of serious coronary insufficiency; if the clinical history is distinctive of angina pectoris, this must be a simultaneous diagnosis.

Similarly many of the other diseases sometimes associated with pain in the chest are improperly considered the cause of angina pectoris in a given patient because they are readily demonstrable by roentgen rays or other objective means, while the coronary disease which is really responsible for the angina pectoris may present no objective abnormalities. I have frequently observed duodenal ulcer and angina pectoris due to coronary artery disease in the same patient. A careful history usually distinguishes the two etiologically different forms of pain. I have also seen patients with a proved paraesophageal hernia in whom angina pectoris was attributed to this lesion; subsequent electrocardiographic studies in one case and postmortem examination in another provided proof that severe coronary disease was the underlying cause.[50a]

Differentiation of Angina Pectoris from Pain Due to Skeletal Lesions. Various forms of cervicodorsal neuritis may produce pain which is mistaken for angina pectoris. This pain is rarely retrosternal, is usually sharp or aching in quality and has no paroxysmal relation to general bodily exertion. One fairly common and often unrecognized cause of pain referred to the precordium and left arm is a traumatic or postural strain of the muscles and ligaments about the lower cervical and upper dorsal spine. An underlying spondylitis or other lesion of the vertebrae or articulating surfaces may also be present.[57] There is often a history of stiff neck. The disturbance may also cause occipital headache or pain of the upper back. But the chief pain is usually in the left shoulder, arm, forearm, fingers and upper precordium.[33] Relief of the pain may be obtained by the application of a cervical collar supporting the skull or by suspension in traction. Semmes and Murphy[77] described a syndrome simulating angina pectoris and characterized by pain in the neck, left shoulder and arm and precordium and by sensory changes in the index and middle fingers, due to unilateral rupture of the sixth cervical intervertebral disk. The pain was due to compression of the seventh cervical nerve root on the left side. Cure or relief was effected by subtotal hemilaminectomy under local anesthesia.

Sometimes advanced osteoarthritis or destructive lesions of the upper dorsal spine or lesions of the spinal cord or nerve roots produce radicular pains of the precordium.[32, 16] These pains occur in band-like zones which are usually complete and involve the anterior and posterior chest wall, corresponding to

the involved nerve segments. Often there is a similar band-like area of objective hyperalgesia (Head zone) which has a complete or incomplete segmental distribution. Angina pectoris is more apt to produce pain radiations which skip from one root zone to another and its segmental distribution is usually incomplete. The pain due to spinal lesions is not related to general bodily effort but is induced by motions of the spinal column or by factors increasing intraspinal pressure such as coughing and sneezing.[78, 16]

Periarthritis of the shoulder joint, subacromial bursitis and calcification of the shoulder tendons are common lesions, often associated with pain not only about the shoulder but also in the arm and anterior chest wall. When the left shoulder is involved, the pain may be interpreted as angina pectoris. Ordinarily the precipitation or exaggeration of the pain by elevation or rotation of the arm, the limitation of motion about the shoulder, and the absence of relationship to walking distinguish the pain due to these lesions from that of angina pectoris.

However, the differential diagnosis is often complicated because of the frequent association of disease of the shoulder region and angina pectoris. Furthermore the shoulder disturbances are not infrequently the consequence or sequel of a previous acute coronary occlusion (see p. 460). Therefore the orthopedic or roentgenologic demonstration of bursitis, calcification or periarthritis of the shoulder should not be interpreted as a complete explanation for the patient's pain without a careful clinical history and examination, and a roentgenologic and electrocardiographic study of the heart to determine or exclude the presence of associated angina pectoris and coronary or other cardiac disease.

Occasionally pain in the left upper extremity and precordium is due to compression of fibers of the brachial plexus by a *cervical rib* or against the first thoracic rib (*scalenus anticus syndrome*). In the latter syndrome a high fixation of the ribs and sternum or a low position of the shoulder and brachial plexus leads to irritation and stimulation of the plexus with secondary spasm and shortening of the scalenus anterior.[58, 61] This causes further elevation of the first rib and compression of the brachial plexus. The pain in the precordium and arm is sharp or aching and often radiates to the fourth and fifth fingers. It may be associated with numbness, tingling or other paresthesias. Relief of the pain by the injection of novocain into the scalenus anterior muscle is helpful in the diagnosis. The presence of cervical rib is demonstrated roentgenographically. Cure is effected by surgical removal of the cervical rib or by resection of a portion of the scalenus anterior muscle, depending on which is the cause of the pain.

PROGNOSIS

The prognosis of angina pectoris is essentially that of the causative underlying disease. This has been discussed in the individual chapters on coronary artery disease, aortic insufficiency, aortic stenosis, syphilitic heart disease, etc. In general, angina pectoris associated with syphilitic heart disease has a more serious prognosis than when associated with severe coronary disease. Syphilitic aortitis with angina pectoris occurring at night and in the recumbent position has a particularly unfavorable outlook. Angina pectoris in cases of calcific aortic stenosis is usually a late symptom, and the duration of life after its onset is brief. The development of angina pectoris in young subjects with rheumatic

aortic valvular disease is particularly ominous, although occasionally the anginal paroxysms subside. In the largest group of cases of angina pectoris, those due to coronary arteriosclerosis, the prognosis is more encouraging than in the groups due to the other major causative diseases. When there is a definitely remediable contributory factor such as anemia or hyperthyroidism, the outlook may be more favorable than in the absence of such factors. Sometimes the cure of a contributing causative factor may lead to the complete disappearance of the paroxysms of angina pectoris.

The danger of sudden death is an intrinsic element of the syndrome of angina pectoris and compels a note of caution and reserve in any attempt at predicting the outcome. Sudden death occurs in about 10 to 15 per cent of cases; in a much larger percentage of cases death is not sudden but unexpected and rapid after a brief manifest attack of myocardial infarction. Sudden death is believed to result usually from ventricular fibrillation, to which the anoxic myocardium or heart with diminished coronary reserve is particularly susceptible. However, it is not understood why the occurrence of sudden death is not clearly correlated with the frequency or severity of the anginal attacks, and it is impossible to prognosticate from either the clinical history or findings which patient with angina pectoris will die suddenly.

The advent of angina pectoris does not forebode imminent demise. Most patients live for five to ten years after the onset of this symptom. Earlier estimates of duration of life averaging four to five years[91, 20] have been revised progressively upward by recent studies. Of about 500 patients followed by White et al.[92] 90 per cent succumbed after an average period of eight years following the onset of symptoms. Those still alive had survived for an average interval of 18.4 years. In another follow-up study of 3440 cases of angina pectoris, 18 per cent succumbed in the first year after onset; thereafter there was an average annual mortality rate of 10 per cent for those surviving at least three years.[63] Like others,[90, 56] I have seen many patients who have survived for more than ten years, and occasionally for more than fifteen or twenty years.

The hereditary factor sometimes appears important in prognosis. A history of angina pectoris and coronary thrombosis in many members of the family, especially in the parents, with death at an early age, bespeaks an unfavorable and brief course. The age of onset is significant in that the earlier the onset, the lower the age at death, even when the duration of angina pectoris is relatively long. Furthermore, when angina pectoris begins in the thirties or forties, it often denotes an hereditary vascular weakness and a likelihood of early complications and death. Pronounced hypertension or cardiac enlargement, previous myocardial infarction and heart failure are among the associated findings which tend to diminish the duration of survival, but there are numerous exceptions.

The progress of cases of angina pectoris may follow any one of many courses. Sometimes, with or without a significant change in the severity or frequency of the attacks, the patient dies suddenly months or years after the initial paroxysm. More commonly, the course of the disease is punctuated by one or more clinically diagnosed attacks of acute myocardial infarction before death supervenes. This occurs in at least 25 per cent of the cases of angina pectoris. In some instances there is no positive evidence of an acute myocardial infarction, but a sudden sharp increase in the frequency and severity of the anginal paroxysms suggests strongly that a large coronary vessel has become occluded.

In a large number of cases, the clinical course is characterized by the gradual or sometimes sudden development of congestive heart failure, usually late in the course of the disease. As a rule it may be assumed, although this is not always clinically apparent, that the failure appeared after the closure of additional coronary vessels and a consequent extension of myocardial damage. In still other cases an associated hypertension and diffuse arteriosclerosis determines the ultimate outcome; the patient eventually succumbs to cerebral thrombosis or embolism, cardiac failure or renal insufficiency. Finally some patients never develop any serious complications referable to their underlying cardiac disease but die of intercurrent infections, carcinoma or other independent disease.

Angina pectoris may disappear for long periods of time or permanently, even after it has been present for months or years. Often this denotes that the living area of myocardium which had previously suffered recurrent anoxia and thereupon had engendered pain has finally been destroyed and undergone fibrosis as a result of a complete coronary occlusion. Following a clinical attack of acute myocardial infarction the patient may be able to resume moderate activity without recurrence of pain even with exertions that formerly produced it. The converse has also been noted, i. e., the onset of angina pectoris following a clinical episode of myocardial infarction. Angina pectoris almost always subsides or disappears completely with the development of congestive heart failure or permanent auricular fibrillation. This may be explained by the reduction in activity which these complications impose or by the fact that they usually appear after an acute coronary occlusion with death of the pain-producing myocardial tissue. The disappearance of angina pectoris after correction of anemia has been mentioned.

The patient with angina pectoris may be hardly inconvenienced or his activity may be involuntarily so restricted that he is a chronic cardiac invalid. Most patients, for at least a few years after the initial episode, remain outwardly fairly normal individuals, capable of conducting their business or profession on a somewhat diminished scale of activity, or of earning their livelihood at their usual occupation.

TREATMENT

The treatment of angina pectoris is designed primarily to prevent or reduce the frequency of attacks; the paroxysm itself usually requires no special treatment as it is brief in duration and subsides spontaneously. Occasionally, however, specific therapy is indicated to prevent an attack or to relieve pain which occurs frequently even with the patient at rest. The prevention of attacks of angina pectoris depends on the treatment of the underlying or contributing causative diseases and the elimination or cure, when possible, of the factors which initiate or contribute to the precipitation of the paroxysms.

Management of the Underlying Disease. The primary approach in the treatment of any given case should be the determination and proper management of the underlying cause. This is discussed under the respective headings: coronary artery disease, syphilitic heart disease, aortic valvular disease, etc. Unfortunately, with the possible exception of the treatment of syphilitic heart disease, the measures available or recommended in the treatment of the causative diseases are of little therapeutic efficacy. Measures to improve the basic deficiency in blood supply to the heart are discussed later in this chapter.

Treatment and Elimination of Contributing Factors. The administration of liver extract in pernicious or other primary anemias, of iron in the iron-deficiency anemias or transfusions in anemia due to acute hemorrhage may prevent entirely the occurrence of angina pectoris, even through the basic underlying coronary disease or valvular disease is unaffected. In addition it may be necessary to treat the original cause of a secondary anemia when this can be discovered: e. g., bleeding hemorrhoids, peptic ulcer, fibroid uterus or improper diet. Similarly, in cases of angina pectoris with hyperthyroidism, the latter should be corrected (p. 925).

Although the relation of *disturbances of the gastrointestinal and biliary tract* to angina pectoris is still uncertain, their correction may be followed by an amelioration or disappearance of cardiac pain. A rigid treatment of peptic ulcer or of functional pylorospasm and gastric hyperchlorhydria by bland frequent feedings, alkalis and sedatives not only relieves the ulcer symptoms but may reduce the frequency of angina pectoris. When symptoms are caused by a diaphragmatic hernia, they may be controlled by small meals, antispasmodics, and the maintenance of the erect position for one-half hour or longer postprandially. Rarely operative correction is necessary and may also alleviate anginal pain.[60]

Cholelithiasis and chronic cholecystitis are often asymptomatic, especially if the intake is moderate in amount and bland in quality. However, often the severity and persistence of symptoms warrant surgical removal of the gallbladder. Cholecystectomy in such cases has been reported as alleviating not only the symptoms referable to the gallbladder but also the anginal symptoms. This surgical procedure has been followed in some cases by the disappearance of electrocardiographic abnormalities.

The eradication of *foci of infection* such as a diseased tooth, or the alleviation of other painful somatic foci to which anginal pain is referred or which help to bring latent painful cardiac impulses to the clinical level, may be followed by a disappearance or diminution of attacks of angina pectoris.

Although there is no convincing proof that *tobacco* directly causes angina pectoris, it is my custom to urge that patients stop smoking when they first consult me for angina pectoris. If the attacks are not diminished even after the omission of tobacco, some patients resume moderate smoking without apparent harm and I do not insist on the prohibition. Often patients feel better, generally, after foregoing tobacco, even when there is no striking causal relationship between smoking and cardiac pain.

Avoidance of Precipitating Factors. Patients with angina pectoris rapidly learn by themselves to avoid those forms of bodily exertion which are the commonest immediate causes of pain. Usually it is necessary to reduce the distance and especially the speed of walking. To avoid being conspicuous, many patients stop repeatedly in front of stores and pretend they are window shopping. Often the patient may avoid pain by changing his manner of transportation so as to reduce the walking distance to his train or subway. He may have to change his route if it involves walking uphill. Running for buses or trains must be prohibited. The patient must learn to allow sufficient time so that hurrying is unnecessary. Occasionally patients find that if they walk a block until mild pain develops and rest long enough for it to subside, they may then walk moderate distances without discomfort. Walking after meals is completely prohibited; if essential occasionally, the meal should include minimal quantities.

I have seen patients whose pain, after walking, occurred only on their way to the train in the morning. However, by postponing breakfast until they arrived at a restaurant within a block or so of their office, a paroxysm of angina pectoris was avoided. Walking in cold weather, especially against the wind, should be avoided when possible. If feasible, the coldest month or months of the year should be spent in a warm climate.

Other activities which induce pain should be determined by a careful detailed diary kept by the patient. Such studies will teach the patient what he may do and what he should avoid, and will permit the physician to make practical suggestions. Except for walking rapidly or far, many patients will find that they can continue their gainful occupation, sometimes even when this involves certain forms of physical work such as carpentry, painting or plumbing. Sudden and unusual forms of physical exertion and hard physical labor should be interdicted.

Other precipitating factors which should be avoided are discussed below under general measures and include heavy meals, emotional outbursts, prolonged conversation especially on controversial subjects, straining at stool and other activities which produce pain in individual patients. Some patients may find relaxation in playing cards but most experience excessive emotional tension even when the stakes are small. The effect of watching competitive sports or horse racing must be carefully evaluated. Golf is permissible if the patient enjoys it and suffers no pain when playing. Caution should be exercised in the administration of insulin to patients with coronary disease, as hypoglycemia may induce an attack of angina pectoris. Similarly, epinephrine may provoke anginal pain when used diagnostically or in the treatment of bronchial asthma in patients with a diminished coronary reserve.

General Management

Bed rest is ordinarily not required in the treatment of angina pectoris. However, if a patient consults me promptly after his first attack of angina pectoris, I often advise a period of bed rest or great limitation of activity for one to two weeks, for the sudden development of angina pectoris often denotes the occurrence of an acute coronary occlusion without myocardial infarction. Occasionally attacks of angina pectoris occur so frequently, and with such slight bodily exertion, that the patient is compelled to rest in bed. The patient should be instructed to summon his physician if the pain persists for more than fifteen minutes or if it is more intense and different from previous attacks. While those forms of activity which induce attacks should be avoided, it is often possible for the patient to take certain forms of *exercise* or to take them at certain times of the day without discomfort. He should be encouraged to promote this muscular tone and general state of fitness by means of exercise which does not provoke pain or dyspnea.

The *psychologic approach* to the patient with angina pectoris and the *regulation and modification of his work and daily activities* are important elements in his treatment and must be carefully adjusted to individual patients. The layman is often aware that angina pectoris connotes the possibility of sudden death; therefore the term should be avoided entirely in a discussion of his disease. The patient's cooperation can usually be obtained if he is informed that the circulation to the heart is impaired. But it is often desirable

to explain the patient's exact cardiac status and possible dangers to the patient's nearest relative. At the same time that the patient is made aware of his disability and the necessary modifications in his manner of living, he should also be assured of the probability of a long and useful life if he cooperates in treatment. Many a patient draws extraordinary optimism from the statement that cardiac patients often outlive subjects with a more favorable outlook simply because they lead a more moderate life. It is the physician's task, by encouragement and ingenuity, to teach the patient to adopt a philosophical attitude to his illness and to accept cheerfully the necessary adjustments in his activity and outlook.

The general questions of *occupation, hours of work, vacations,* etc., must be answered differently in individual cases, according to variations in the severity and frequency of the attacks, the patient's station of life, economic status, education and skills, and the character of the underlying disease. Activity and gainful employment must be restricted more in patients with frequent and intractable pain on the slightest exertion, than in those with occasional and mild attacks. In those with less severe disease and less frequent attacks a careful scrutiny and analysis must be made of the patient's work and other daily activities in order to ascertain his capacity for activity and the factors which induce symptoms; his regimen must be adjusted according to the findings.

Long hours, especially when they involve continuous work under tension, must be avoided. Rest periods during the working day, especially after luncheon, are desirable when feasible; if possible also, long week-ends or a midweekly day of rest should be encouraged. As a rule the patient should retire early and a restful night should be assured if necessary by the administration of soporifics before retiring or of mild sedatives during the day. In large organizations it is sometimes possible and desirable for the patient to change his job to one which is less trying, even if this transfer entails a moderate reduction in income. Sometimes it is necessary to perform only part-time work and in some instances to alter the occupation completely.

Vacations are essential and, if manageable, should be taken at least twice a year. It is advantageous to take vacations during the extremes of hot and cold weather and to choose resorts in climates which avoid these extremes. On the European continent and to less extent in this country, patients with angina pectoris were wont to visit various spas both for treatment and for a vacation. While such visits were frequently rewarded by therapeutic benefits, these were due chiefly or entirely to the pleasant surroundings and the surcease from business and domestic stress rather than to any specific curative properties of mineral waters or baths. The well-regulated regimen as to diet, exercise, bowel habits and sleep is more likely to be followed in the environment of a spa than at home or even in an ordinary resort. However, the relaxation and change of environment which are usually associated with a vacation in any pleasant surroundings are of sufficient value, and are often preferable to a long, inconvenient and usually expensive trip to some famous spa. Because of the reduction in oxygen tension at high altitudes, vacations in mountainous regions far above sea-level are undesirable, at least theoretically, but I have known patients who have done well at places like Colorado Springs which has an altitude of 7000 feet. Similarly there is a theoretical objection to airplane travel which is usually at 5000 to 10,000 feet, and especially to stratospheric or

substratospheric flying in transcontinental trips. Oxygen should be used when flights are made at heights exceeding 7500 feet, but especially above 10,000 feet. Most patients with angina pectoris tolerate usual commercial flights.

For those patients who are compelled or prefer to retire completely from work, some program should be formulated to avoid ennui if not actual depression. The resumption of an old hobby or the development of a new one is particularly desirable. This often provides a test for the physician's initiative, ingenuity, persuasiveness and enthusiasm. The radio and the movies are often sought to fill the days and evenings. Considerable discretion and censorship may be necessary to choose programs which amuse and relax and do not bore or excite. Card playing may be a pleasurable form of diversion, but in general play for stakes of any kind should be prohibited. Patients who become too excited even when no stakes are involved should not play at all.

Diet. There is no specific dietary treatment for patients with angina pectoris. The diet depends on associated factors. In general a low calorie diet is desirable, especially if the patient is overweight. It is particularly advisable to divide the dietary intake into small meals which may be taken more frequently than the usual three times daily. In the presence of associated biliary tract disease or a peptic ulcer, appropriate dietary measures should be instituted. Functional gastrointestinal disturbances, characterized by flatulence, postprandial distention and gaseous eructation, should be treated by a bland diet (low in roughage, elimination of raw fruits, fried foods, gravies, pastries, cabbage, onions, corn and other gas-producing vegetables).

Bowels. Regularity of bowel habit, always desirable, is particularly important in these patients, for colonic stasis and associated flatulence often help to produce attacks. Mild laxatives may be given if necessary. Excessive straining at stool should be avoided.

Tobacco (p. 389).

Coffee and Tea. These may be taken in moderate quantities. They have the theoretical advantage of being coronary vasodilators and the disadvantage of provoking nervousness and sleeplessness in some patients.

Alcohol (see drug therapy below).

Drug Therapy

Nitrites. The nitrites, which cause direct coronary vasodilatation (see p. 326), represent the only specific medication in the relief of angina pectoris. As a rule they are used for prompt relief of the pain after the attack develops, but they may also be employed prophylactically.[22] For the latter purpose they are taken before such activities as are known by experience to produce pain. Of course whenever possible it is best to avoid both the precipitating factor which causes pain and the nitrites. Under no circumstances should the nitrites be taken to permit the patient to perform some unusual strenuous activity which is likely to cause harm.

Nitroglycerin is the drug of choice, since it is cheap, convenient to take and, next to amyl nitrite, acts most rapidly. It is administered in tablets which the patient is instructed to dissolve under the tongue. If the tablets are not readily soluble, they may be inert or their action delayed. The usual therapeutic dose is 1/100 grain but it is preferable to begin with a 1/200 grain tablet, which often suffices and is less likely to induce uncomfortable side-actions. Its action is noticeable in one to two minutes and continues for fifteen minutes to an

hour. In most cases the relief is striking as well as prompt. Often, however, it may be accompanied by mild fullness, warmth or throbbing in the head. Rarely, in subjects with an idiosyncrasy to the drug, severe headache, faintness or even syncope may occur. Until the effects of the drug are known, it is advisable for the patient to sit down or find some support when he takes nitroglycerin. If after the repeated beneficial use of nitroglycerin the patient suffers an attack of pain which does not respond to this therapy, he should be instructed to cease all activity at once and call his physician. Except when it is used prophylactically, nitroglycerin should not be taken for those attacks which are known to subside promptly with a brief period of rest. Since the pain will disappear rapidly and spontaneously, there is no need for the patient to suffer any unpleasant side actions of the drug.

Amyl nitrite, introduced by Lauder Brunton[12] in 1867, acts more rapidly (in ten to fifteen seconds), but its action lasts only for several minutes. It is administered in small glass pearls or ampules which must be crushed in a handkerchief and inhaled. Its disadvantages are its expense, inconvenience in carrying and administration and the distinctive odor which calls undesired attention to the patient when it is taken in the presence of others. Its unpleasant side-actions are similar to those of nitroglycerin.

Other nitrites are rarely used or indicated. *Sodium nitrite,* administered orally in tablet form, in doses of 0.03 to 0.06 gram (½ to 1 grain) requires ten to fifteen minutes for an effect which continues for an hour or longer. *Erythrol tetranitrate,* which may be given orally as tablets in doses of 0.015 to 0.030 gram (¼ to ½ grain) requires fifteen minutes for effect, the duration of which is several hours. When nitrites are given prophylactically at regular intervals throughout the day to patients with frequent attacks at rest or on slight unavoidable provocation, these longer acting nitrites may be preferred. Similarly *mannitol hexanitrate* and *mannitol pentanitrate,* the action of which is even more delayed and prolonged, may be given in ¼ to ½ grain doses for prophylactic effect.

Recently a volatile liquid nitrite, *octyl nitrite,* prepared by Krantz, Carr and Forman[38] and administered by inhalation, was found to be an effective agent in preventing or sharply abbreviating the duration of attacks of angina pectoris.[26] It is available commercially in capped glass inhaler tubes (octrite inhalers). After the cap is unscrewed, the tube is inserted into one nostril while the other is closed and the patient takes one moderately deep inhalation; rarely more than one inhalation is necessary. It is superior to nitroglycerin in that it is more rapidly absorbed (ten seconds) and its effect is apparent in thirty seconds; its advantage over amyl nitrite is its lower cost. On the other hand, the patient requires careful instruction as to its use. The tube often breaks and is not available as promptly as it should be because of its cap arrangement. It is more expensive than nitroglycerin. Its unpleasant side-actions are similar to those of nitroglycerin or amyl nitrite and are more likely to occur because of inaccurate dosage.

Xanthines. Members of the xanthine group of drugs, usually compounds of theobromine or theophylline, are widely employed in cases of angina pectoris due to coronary disease, despite considerable disagreement as to their clinical effectiveness.[11] Their use is based on experimental observations indicating that these drugs produce coronary vasodilation and an increased coronary flow in isolated perfused hearts, heart-lung preparations or in the intact animal

However, when the dosage of drug administered and the amount and transiency of increased flow are considered, it is questionable whether these experimental observations form an adequate basis for anticipating clinical benefit in human cases of angina pectoris. The observations of Fowler, Hurevitz and Smith[24] that aminophylline (theophylline ethylenediamine) reduced the size of myocardial infarcts after coronary occlusion in dogs appeared to give further justification for the use of the xanthine drugs in coronary disease, but Gold, Travell and Modell[30] were unable to confirm the experimental results of Fowler and his associates.

More direct observations of the effect of the xanthine drugs on human subjects with angina pectoris are difficult to evaluate because of the subjective and variable character of the symptoms and differences in the criteria for its diagnosis and variations in dosage of drugs employed. Since Askanazy[2] reported the disappearance of attacks of angina pectoris following the administration of theobromine (diuretin), favorable results were noted by Gilbert and Kerr[28] with theobromine sodium acetate, by Smith, Rathe and Paul[79] using theophylline, and by Le Roy[40] who employed aminophylline. On the other hand, in controlled studies on patients with angina pectoris who were given xanthine drugs alternating with other coronary dilators and placebos, Evans and Hoyle,[22] Master, Jaffe and Dack,[51] and Gold, Kwit and Otto[29] were unable to demonstrate any significant benefit from the xanthine drugs. Improvement following xanthine drug therapy has also been reported on the basis of objective criteria, such as exercise tolerance before and after medications,[71, 55, 25, 4] the tolerance to induced anoxemia[45] and the effect on electrocardiographic abnormalities.[93]

Unfortunately the clinical course of angina pectoris is too variable to permit rigid conclusions even on the basis of objective findings such as these. The reports as to the effectiveness of the xanthine drugs are contradictory and the evidence for their benefits on the clinical course of angina pectoris is not impressive. Yet the negative reports are no more convincing. For the present, it seems justifiable to conclude that the experimental and clinical observations are sufficient to warrant the continued administration of the xanthine drugs to patients with angina pectoris. In my own practice, these drugs are subsidiary to the use of nitrites and sedatives; I often prescribe a xanthine drug early in the treatment of a patient and later discontinue its usage if neither the patient nor I can observe any beneficial effect. In other cases the xantnines are continued for many years, usually because the patient is convinced of their value and I cannot disprove his belief.

The xanthine drugs most commonly used are: aminophylline (theophylline with ethylenediamine), theophylline with sodium acetate, theophylline with calcium salicylate and theobromine with sodium acetate. Aminophylline is sometimes administered rectally in the form of suppositories (0.3 to 0.5 gm.) each. In the absence of cardiac asthma there is no advantage in intravenous therapy but the intravenous administration of aminophylline may help to control nocturnal paroxysms of cardiac pain. As a rule the xanthine drugs are given orally in the form of enteric coated tablets or capsules. These coatings are used to avoid the gastric distress, such as heartburn and nausea, which otherwise are frequent complications. For the same reason, these medicaments are taken during meals. It is important to prescribe adequate doses; the doses commonly

given are insufficient and do not provide a fair test of the drug's efficacy. The following are some of the xanthine derivatives used and their dosage:

Theobromine and sodium acetate—0.5 to 1.0 gm. four times daily;
Theocalcin (theobromine-calcium salicylate)—0.5 to 1.0 gm. four times daily;
Aminophylline (theophylline ethylenediamine)—0.1 to 0.2 gm. three or four times daily.

Many of the xanthine drugs have been marketed in combination with sedatives, usually with phenobarbital. The chief disadvantage is the rigidity imposed on the relative dosage of the two components; in particular, the dose of phenobarbital often needs to be altered for different patients and even for the same patient at different times.

Sedatives. Sedatives are among the most widely prescribed drugs in the treatment of angina pectoris. Their purpose is to allay anxiety and minimize the emotional reactions which may precipitate attacks of pain. *Phenobarbital* in doses of 0.015 to 0.03 gm. (¼ to ½ grain), three times daily, is employed most frequently, sometimes in combination with a xanthine derivative. *Bromides* in doses of 0.3 to 1.0 gm. (5 to 15 grains) and *chloral hydrate* in 0.3 gm. (5 grain) doses, alone or in combination, three times daily are among other sedatives often administered. It is often necessary to prescribe soporifics for sleeplessness, e. g., seconal, 0.1 to 0.2 gm. (1½ to 3 grains); nembutal, 1½ to 3 grains; or veronal, 0.3 to 0.6 gm. (5 to 10 grains) on retiring. Opiates are not indicated in the treatment of angina pectoris because the recurrence of attacks would tend to lead to addiction. If pain is persistent and unrelieved by nitrites, the probability of myocardial infarction or some other cause should be considered. In the occasional instances of very frequent paroxysms even at rest, alcohol block or section of the nerve fibers may be necessary (p. 396), Cobra venom has been recommended to allay pain in such cases[34] but has failed in a few instances in which I have tried it.

Other Drugs. *Alcohol* is often prescribed in ½ to 1 oz. doses, both for the prevention and relief of attacks. It is the oldest drug used for this purpose, since its benefits were mentioned in Heberden's original description. However, it is doubtful that alcohol has any direct value in the prevention or alleviation of the anginal paroxysms.[80] While I always permit and usually advise the ingestion of moderate amounts of alcohol by patients with angina pectoris, especially elderly patients, I do so more for its beneficial effect on general well-being than for any dramatic improvement in the angina pectoris itself. On the other hand I have seen many patients who have been made worse by an overenthusiastic indulgence in alcohol. This applies particularly to patients with peptic ulcer or other gastrointestinal disturbance.

Trichlorethylene has been employed for the relief and prevention of attacks of angina pectoris.[48] It is administered by inhalation, three inhalations being taken after crushing a glass ampule containing 1 cc. of the drug. Any beneficial effect is not dependent on coronary vasodilatation but on its anesthetic, analgesic or sedative action. Occasionally it may cause a brief loss of consciousness.

Digitalis is not indicated in the treatment of angina pectoris unless heart failure or rapid auricular fibrillation is present, and each of these complications is infrequently associated with angina pectoris. Some of the nocturnal attacks

of angina pectoris, occurring when the patient is recumbent, are due in part or entirely to left ventricular failure. These may be alleviated by digitalization, rigid sodium restriction, the administration of aminophylline 0.25 gm. intravenously before the patient retires, and by the use of mercurial diuretics.

Quinidine has only recently been suggested as a therapeutic agent in the treatment of angina pectoris[25] but there is insufficient clinical data for its evaluation in this capacity. Proger and his associates[66] reported that quinidine exerted a beneficial effect on angina pectoris when attacks were precipitated or increased in frequency by a cardiac irregularity.

Antithyroid drugs (thiourea derivatives) have been administered in order to reduce the patient's metabolism and thereby diminish the work of the heart and its need for coronary blood flow. Numerous reports have appeared of improvement in persons with angina pectoris, following the use of thiouracil[67, 70, 7] propylthiouracil[35] and methylthiouracil.[76] The disadvantages of these drugs, including toxicity, need for close supervision and prolonged treatment and temporary effect, have also been documented.[17] It is doubtful that they will play a significant role in the treatment of angina pectoris.

Papaverine has been recommended in oral doses of 0.1 gm. four times daily on the basis of its coronary vasodilator effect in animals and its sedative action.[19] A beneficial result in patients with angina pectoris has not been demonstrated.

Khellin, an extract of seeds from an Eastern Mediterranean plant, long used as an antispasmodic for ureteral colic, was recently found to be a potent coronary vasodilator. Favorable results in the treatment of angina pectoris have been reported when the drug was injected intramuscularly in 100 mg. doses or given orally in 50 to 100 mg. doses three times daily.[1]

Testosterone. Favorable results have been reported by a number of observers[18, 41, 82] but not by Levine and Likoff.[43] The benefits of testosterone are usually not specifically related to the cardiac pain.

The claims that vitamin E (alpha tocopherol) has therapeutic merit in cases of angina pectoris and other forms of heart disease have not been confirmed.[44, 49]

Nicotinic acid has been administered as a continuous intravenous drip infusion containing 100 to 300 mg.[59] Tissue extracts, including those from the pancreas, unfortunately termed "heart hormones," have proven ineffective. The iodides are still widely prescribed for angina pectoris but, except in cases due to syphilitic ostial stenosis, there is no sound basis for their usefulness in this condition. Epinephrine, ephedrine and other sympathomimetic drugs should not be given.

Physiotherapy and balneotherapy have been used in the treatment of angina pectoris, especially at various spas. There is no acceptable evidence of their specific value or of the value of diathermy to the chest wall. Roentgen ray therapy to the adrenals has been used to diminish acute discharges of epinephrine.[68] There is insufficient evidence to recommend its employment.

Paravertebral Alcohol Injections

In a small percentage of cases of angina pectoris the attacks recur with such frequency and the relief from multiple daily doses of the nitrites is so transient and incomplete that it is necessary to resort to opiates. For such cases, excellent results can often be obtained by paravertebral alcohol injections[50, 83] which block the painful impulses from the heart. The points at which anesthesia is

effected are the upper five or six thoracic sympathetic ganglia and their adjacent rami communicantes through which the painful impulses eventually pass (see p. 371).

Satisfactory results have been reported by Levy and Moore[46] in 45 patients and by J. C. White and Bland[88] in 75 patients. Good results with virtually complete relief of pain were obtained in 56 per cent of the latter series, a reduction in the severity of pain in 21 per cent and no appreciable result in 8 per cent. Although many of these patients were extremely ill, there was only a mortality of 8 per cent within two weeks of the procedure. In 40 cases there was no recurrence for periods up to nine years but in 14 pain reappeared within two and one-half months to five years.

The advantage of the procedure is the ability to perform it without a general anesthetic and with minimal discomfort to the patient and only slight risk. However there is need for practice and skill; in 10 to 20 per cent of the attempts, a successful nerve block is not obtained. The most common complication is a painful intercostal neuritis due to the alcohol injected. It usually clears in a few months but may be more persistent and so severe that the posterior nerve roots must be sectioned. Occasionally there is accidental injury to the pleura with consequent pleuritis, pleural effusion or pneumothorax, and rarely injury to the spinal cord structures.

The *technic of paravertebral alcohol injection* as described by White and Smithwick[89] and by Levy and Moore[46] is as follows:

The patient is given a sedative the night before and on the morning of the injection; also 1/100 grain of atropine is administered hypodermically to exclude vagovagal reflexes. The patient is injected in his own bed, while lying on the side opposite that to be injected. His knees are drawn up and his head bent forward and supported by a pillow, as for a spinal tap. The highest prominent vertebral spine is the seventh cervical vertebra. This and the spinous processes below, down to the fifth thoracic, are the bony landmarks. Each of these spinous processes is at the same horizontal level as the transverse process and angle of the rib below. The injections are made from 3.5 to 4 cm. lateral to the spinous process on the side of the pain, at the levels of the seventh cervical and upper four dorsal spines.

By means of a fine hypodermic needle intracutaneous wheals are made at the sites of injection. Then needles 10 cm. long are inserted through these wheals perpendicular to the surface of the back and at a depth of 3 to 3.5 cm. until they touch the upper four transverse processes or the articulating portion of the ribs. These needles should be made of rustless flexible steel; thin lumbar puncture needles or special Labat needles may be used. Markers of narrow rubber tubing are placed on the needles in order to measure the depth to which the needles are inserted. Having been inserted to the point mentioned, the needles are then inclined slightly caudally so as to touch the lower border of the transverse process or angle of the rib. The depth marker is then pulled up so as to be 3 cm. from the skin. The needle is directed medially at an angle of 20° and inserted 3 cm. until it is felt in contact with the lateral surface of the body of the vertebra. If contact is made at a lesser depth, the needle should be directed less medially. The total depth of insertion through the skin varies from 5 to 6 cm. in thin persons to 8 to 10 cm. in patients with a thick chest wall.

After insertion of the needles, aspiration is performed to exclude the possibility that the needle may have entered a blood vessel or the subarachnoid space. If this occurs, the needle is withdrawn and its direction altered. When the needles are properly placed, 2 cc. of 2 per cent novocain is injected through each. Within ten minutes anesthesia should be effected in the axilla, the inner surface of the arm and over the third and fourth ribs anteriorly and posteriorly. A Horner's syndrome and anhydrosis of the arm and side of the head and neck usually appear with proper anesthesia. The hand, and usually the neck and face, feel hot and dry. When this preliminary anesthesia has been accomplished, an additional 3 cc. of 1 per cent novocain is injected at each site to prevent pain from the subsequent injection of alcohol. Finally 5 cc. of 95 per cent alcohol is injected slowly

through each needle, withdrawing the plunger of the injecting syringe each 0.5 cc., in order to be certain that the needle has not slipped into a blood vessel or subarachnoid space. The patient is kept quiet for one hour, lying on his side with his back supported by pillows. He is usually out of bed the following day; if hospitalized for the procedure, he may leave in seventy-two hours.

Surgical Treatment of Angina Pectoris

The various surgical procedures advocated for the treatment of angina pectoris were designed either (a) to interrupt painful impulses by cutting sensory fibers in the sympathetics or their attachments to the spinal cord, (b) to diminish the work of the heart by total thyroidectomy, or (c) to promote the development of a collateral circulation to the heart.

Earlier operations on the cervical sympathetic chain[37] or ganglia[39] or stellate ganglia[15] gave inconsistent results because they only partially interrupted the sensory pain fibers from the heart. Based on the knowledge that all painful impulses from the heart eventually pass through the upper four or five thoracic ganglia, their rami communicantes and the corresponding thoracic posterior spinal nerve roots, successful results in relieving angina pectoris have been obtained either by (a) surgical excision of the upper four or five thoracic sympathetic ganglia or (b) section of the upper four or five dorsal roots (posterior rhizotomy).

White and Bland[88] reported satisfactory relief with the former procedure in 8 cases with one death. Lindgren and Olivecrona[47] reported a series of 71 patients in whom stellate ganglionectomy and the removal of the upper three or four thoracic ganglia was performed for angina pectoris with complete relief in 44 per cent, substantial relief in an additional 41 per cent, unsatisfactory result in 7 per cent and 6 deaths within one month of the operation. Pain in the neck or jaw was not relieved. Occasionally there was a postoperative pain in the arm ("traumatic neuritis") which usually was mild, but in one case required a posterior root section for relief.

In cases with bilateral pain a posterior rhizotomy may be preferable because the dorsal posterior roots on both sides can be sectioned at a single operation. This is a more formidable operation than ganglionectomy because an extensive laminectomy must be performed. Both types of operations are rarely indicated.

The *operation of total thyroidectomy*[10] was designed to ameliorate angina pectoris by diminishing the work of the heart and for other theoretical reasons, and some satisfactory results were reported.[64] However it has almost been abandoned both because of unproven effectiveness and certain disadvantages of the operation.

The *development of a collateral blood supply to the heart* by surgery is designed not merely to relieve the symptoms of angina pectoris but also to alleviate the underlying circulatory disturbance in the heart. Several procedures have been used:

(1) Grafts of intercostal muscle[5] or of omentum[62] have been sutured to the heart in the hope that extracardiac vessels in these structures would form functioning collateral channels to the heart.

(2) Pericardial adhesions have been produced by irritants to the epicardium[75] or by the instillation of talc into the pericardial cavity.[84] These procedures are designed to promote intercoronary anastomoses and pericardial vascular anastomoses with the coronary arteries.

(3) Ligation of the great cardiac vein with or without pericoronary neurectomy[23] has been performed. This was based on observations that preliminary ligation of the coronary sinus in dogs greatly diminishes the incidence of death or myocardial infarction after subsequent experimental ligation of a coronary artery.[31]

(4) A new branch from the aorta was grafted to the coronary sinus.[6] Direct implantation of the internal mammary artery into the myocardium was suggested on the basis of observations on dogs.[86]

All of these procedures are still in the experimental stage.

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19

ACUTE CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

Etiology, Pathologic Physiology and Pathology

Coronary thrombosis refers to the disease associated with an acute thrombotic occlusion of a major coronary artery. The thrombosis is almost always a complication of coronary arteriosclerosis and is an intrinsic stage of the arteriosclerotic process. Acute *coronary occlusion* is a more inclusive term denoting the sudden obstruction of a coronary artery, either by the development of a thrombus or by an intimal hemorrhage with swelling of the arterial wall, or by an embolus.

Myocardial infarction signifies the necrosis or death of a portion of heart muscle because of an interruption or curtailment of its blood supply. While it is usually the result of an acute coronary occlusion, infarction of the myocardium may also occur without mechanical obturation of a coronary artery, following a sharp reduction in the volume or oxygen content of the coronary blood, due to circulatory or hematologic disturbances. *Cardiac infarction* may be a more accurate designation than myocardial infarction in many instances in which the pericardium and endocardium as well as the heart muscle are affected by the coronary occlusion.

Coronary thrombosis is associated with a distinctive clinical picture, characterized usually by pain in the chest, similar in location and radiation to that of angina pectoris but differing in its greater severity and duration, in its usual independence of exertion and especially in its frequent association with evidences of shock and of acute left ventricular failure, fever, leukocytosis and persistent and progressive electrocardiographic changes. Actually these clinical features are due to myocardial infarction and not to the coronary occlusion as such. Prolonged clinical usage and the usual concomitance of coronary occlusion and myocardial infarction have justified the interchangeable use of these terms when referring to the above clinical syndrome. But for clarity in the interpretation of the clinical and laboratory phenomena it is essential to understand that they issue from the infarcted heart muscle and not from the coronary occlusion, per se.

This distinction is important, for acute coronary occlusion and myocardial infarction are not invariably associated. It is now recognized that coronary occlusion may and frequently does occur without ensuing infarction,[11] and

conversely that myocardial infarction may develop in the absence of an acute coronary occlusion.[27] The same clinical picture is associated with myocardial infarction whether or not the latter is due to an acute coronary occlusion; on the other hand, the above-mentioned characteristic pain, fever, leukocytosis and typical electrocardiographic changes do not follow the occlusion unless myocardial infarction ensues.

Coronary Insufficiency and Coronary Failure. Coronary insufficiency[15, 53] is a term which has been applied to the physiologic disturbance in which the supply of coronary blood or oxygen is inadequate for the needs of the myocardium. But it has also been used to denote a *clinical-pathologic syndrome, intermediate between angina pectoris and acute myocardial infarction.* To avoid confusion in usage the term *coronary failure* has been suggested for this syndrome.[25] (See also discussion on p. 365.)

It is characterized by cardiac pain, which is more intense and prolonged than that of angina pectoris and unresponsive to nitrites, but without significant fever, leukocytosis, increased sedimentation rate or the characteristic serial electrocardiographic changes seen in classic cases of acute myocardial infarction. Usually there are RST segment depressions as may be observed in patients with angina pectoris during an attack of pain or during a positive hypoxemia test. The attack of pain may occur during effort or at rest, with emotion, exposure to cold, a heavy meal, a paroxysmal tachycardia, hemorrhage, shock or any factor which significantly reduces the coronary blood flow or increases the work of the heart. The pathologic basis is either severe coronary arteriosclerotic narrowing or occlusion without infarction, or mild, patchy myocardial necrosis without coronary occlusion.

It is apparent that the variations in clinical pictures of angina pectoris, coronary failure and myocardial infarction correspond to similar variations in the severity and duration of the underlying myocardial anoxia and to absence or presence of significant anatomic alterations. Caution should be exercised in the clinical diagnosis of coronary failure, for attacks of this type are often premonitory of myocardial infarction or represent attacks of coronary occlusion with localized infarcts which do not produce striking changes in a routine electrocardiogram.

Frequency and Importance of Acute Coronary Thrombosis. As heart disease is now the acknowledged greatest single cause of death in this country, so coronary thrombosis is the most important cause of heart disease. The cardiac mortality rate in 1940 was 292.5 per 100,000 population and 25 per cent of this was attributed to disease of the coronary arteries; most of the latter undoubtedly represented coronary thrombosis and its consequences. Another 46 per cent of the cardiac mortality was attributed to chronic myocarditis and myocardial degeneration, which surely includes a large though undefined percentage of cases of acute and chronic coronary thrombosis. Master[59] has estimated that 800,000 attacks of coronary thrombosis occur annually in the United States, which means that after the age of forty, one man in 38 and one woman in 115 sustain a coronary occlusion each year.

The Increased Incidence of Coronary Thrombosis. There has been a progressive increase in the reported, if not the actual, incidence of coronary occlusion and this rising curve of mortality has not yet levelled off. The crude death rate from coronary disease had risen from 7.9 per 100,000 in 1930 to 23.1 in 1935; subsequently this increased to 71.4 in 1940 and 95.2 in 1946. Similar

data on the reported increase in coronary disease have been presented by Denny,[23] Hedley[36] and others. The latter noted an increase of 126 per cent in the reported mortality from acute coronary occlusion in Philadelphia in the five-year interval between 1933 and 1937.

However, there is great uncertainty as to whether this reported increase is real or due to a statistical mirage produced by increased knowledge and more accurate diagnosis of coronary thrombosis and changing fads in medical nomenclature. In particular the increase in the span of life due to the reduction in childhood and other infections, and to other advances in medical knowledge, has brought a larger proportion of the population to the age groups in which death from arteriosclerotic coronary thrombosis is frequent.

ETIOLOGY OF ACUTE CORONARY OCCLUSION

Underlying Causes

Arteriosclerosis of the coronary arteries is responsible for at least 95 per cent of the cases of acute coronary occlusion. In most of these instances of acute arteriosclerotic occlusion, the obstruction is caused by a fresh thrombus which is usually secondary to an intimal hemorrhage in an atherosclerotic plaque, or to rupture of an arteriosclerotic abscess. Less often, the occlusion results from swelling of the arterial wall due to an intimal hemorrhage in a vessel, the lumen of which was already narrowed by arteriosclerosis (see p. 415). The etiology of arteriosclerosis itself has been discussed in Chapter 16, p. 338.

This chapter is concerned essentially with acute coronary occlusion due to arteriosclerosis. Very rarely an acute occlusion is due to other causes which will be mentioned briefly and which have been discussed in the general chapter on coronary artery disease (p. 329).

Syphilitic aortitis is commonly complicated by stenosis or occlusion of the coronary ostia (p. 818). But even these instances of complete occlusion do not fall properly under the heading of acute coronary occlusion because the closure develops slowly and without a sudden incident such as characterizes arteriosclerotic coronary thrombosis. The affected myocardium in cases of syphilitic coronary ostial occlusion usually reveals only ischemic fibrosis with few if any recent foci of necrosis. Only isolated instances of recent myocardial infarction due to syphilitic coronary ostial occlusion have been reported (p. 819). A rare instance of gumma of the coronary artery with myocardial infarction has been documented.[48]

Coronary embolism is the commonest of the rarer causes of acute coronary occlusion (p. 331).

Periarteritis nodosa produces arteritis and aneurysms of the major branches of the coronary arteries in most cases of the disease, but only very rarely does it result in an acute coronary thrombosis and myocardial infarction (p. 330).

Rheumatic fever has rarely been associated with acute coronary occlusion and myocardial infarction in children. It is uncertain whether these occlusions are directly related to rheumatic fever or whether the latter predisposes to premature degenerative (arteriosclerotic) changes. As a rule, the lesions of rheumatic fever are found in the small branches and not in the major coronary vessels, and these lesions are not responsible for myocardial infarction or notable clinical symptoms.[31]

Thromboangiitis obliterans is a rare questionable cause (p. 333). Isolated instances of coronary occlusion due to widespread *tuberculosis* of the pericardium and myocardium, to neoplasms, and to dissecting aortic aneurysm have been reported.

Contributory and Predisposing Factors

Hypertension is the most common disease associated with acute coronary occlusion. Various observers[51, 74, 62] have noted hypertension in one third to three quarters of the cases of coronary occlusion. In my own experience, between one half and two thirds of patients have hypertension at the time of their first clinical attack, but careful studies of the previous history and of postmortem material (e. g., the heart and kidneys) suggest that the percentage is even higher. Lack of uniformity of the statistics on this subject is due in part to varying criteria as to what constitutes hypertension. When a patient is first observed during an attack of coronary thrombosis, a previously elevated blood pressure may have been depressed by the immediate incident or by an earlier unrecognized attack.

Whatever the exact incidence of hypertension in cases of coronary occlusion, it appears to be significantly higher than in the general population. The incidence of hypertension in women with coronary occlusion is definitely higher than among men with this condition. In fact coronary occlusion is extremely uncommon among women in the absence of hypertension.[52] These observations on the incidence of hypertension strongly suggest that it is a significant predisposing factor in the development of acute coronary occlusion. That it is not an *essential* causative factor is proven by the large number of instances of coronary occlusion in patients who have been carefully followed for many years and whose blood pressure has never been abnormally elevated.

The relationship of hypertension to acute coronary occlusion is conjectural since neither the ultimate cause of hypertension nor that of arteriosclerosis is known. It has been suggested (a) that hypertension favors, intensifies or accelerates arteriosclerosis (p. 342); (b) that similar or identical metabolic, endocrine or nervous factors are responsible for both conditions; (c) that simultaneous arteriosclerosis in the kidneys and heart account for the association of hypertension and coronary thrombosis;[22] and (d) that hypertension predisposes to the latter by favoring the occurrence of intimal hemorrhages in arteriosclerotic plaques.[76]

Diabetes. After hypertension, diabetes mellitus is the disease which is most frequently associated with acute coronary occlusion.[95] Root and his associates[86] found a much higher incidence of coronary occlusion in 349 autopsied cases of diabetes mellitus than in the hearts of 1247 nondiabetics. Between the ages of forty and sixty, the frequency of occlusions was 23 per cent among the diabetics as compared to 6 per cent among nondiabetics; between the ages of sixty to eighty, occlusions occurred in 43 per cent of the diabetics as compared with 10 per cent among nondiabetics. Antecedent diabetes has been noted in 10 to 25 per cent of cases of acute coronary occlusion.[51, 6, 62, 68] Among diabetics, coronary occlusion is one of the commonest causes of death.

Diabetes seems to accelerate as well as favor the arteriosclerotic process. Coronary occlusion sometimes occurs in very young diabetics.[83] Like hypertension, diabetes mellitus is encountered in a strikingly higher percentage of females with coronary occlusion than among males. This has been explained

on the premise that arteriosclerosis advances more slowly in women than in men and is therefore less likely to be severe enough to result in an occlusion, unless factors like hypertension and diabetes greatly accelerate its progress. For further discussion and bibliography the reader is referred to Chapter 42.

Familial hypercholesterolemia with xanthomatosis is often complicated by coronary occlusion and acute myocardial infarction (p. 959).

Myxedema (p. 936).

Polycythemia (p. 976).

Disease of the Biliary Tract. A possible relationship to clinical coronary disease was discussed under angina pectoris (p. 363).

Infections. Streptococcal infections[45] and acute tonsillitis[47] are among the factors implicated as contributory or predisposing to coronary sclerosis and acute coronary occlusion. Several times I have seen acute coronary occlusion occur during the course of a pneumococcal or atypical pneumonia. These may merely represent coincidences. The elevation of blood fibrinogen in various infections as well as the occurrence of cold agglutinins in the blood may favor the occurrence of thrombosis. At most, however, these factors are of secondary importance and may be excluded in the vast majority of cases of coronary occlusion. Minkowski[67] found evidence suggesting that infections in infants and children caused coronary intimal thickening which predisposed to arteriosclerosis and thrombosis in later life.

Age. At least 90 per cent of the cases of acute coronary thrombosis and myocardial infarction occur in persons between the ages of forty and seventy. My own experience corresponds with those studies which have revealed a somewhat higher incidence between the ages of fifty and sixty than in any other decade,[62] but others have found the peak between sixty and seventy.[51, 75, 68] As the ability to diagnose acute coronary thrombosis has improved and become widely disseminated, this disease has been recognized with increasing frequency in subjects below the age of fifty and even before the age of forty. The occurrence of this condition in young persons, previously reported as occasional instances, has recently been emphasized by reports of large series of cases, among soldiers between the ages of eighteen and forty.[26, 63, 69, 70, 78, 105] Most of these cases were fatal; as a rule death occurred suddenly and unexpectedly. Probably 5 per cent of first attacks of acute coronary thrombosis occur before the age of forty. Rarely, proven cases have even been observed in childhood and infancy. Thus although acute coronary thrombosis with myocardial infarction is essentially a disease of middle life and thereafter, it may occur at any age, and youth is no contraindication to its diagnosis when the history and findings are characteristic.

Sex. There is a notable preponderance of males among patients suffering from acute coronary thrombosis. Reported series of cases indicate a ratio of males to females varying between 2 to 1 and 6 to 1.[51, 62, 6, 82, 68] The ratio of 3 to 1, based on studies of cases at autopsy, is probably more accurate than the higher ratios reported in clinical series. The preponderance of males is most striking in those cases of coronary occlusion in which there is neither hypertension nor diabetes mellitus.

Occupation. There are insufficient data to permit a definite conclusion as to the etiologic relationship between occupation and the occurrence of coronary thrombosis.[14, 60, 36, 82] It is improbable that occupation is an important predisposing factor. However in the study of coronary artery disease in young

men, Yater et al.[105] found that the affected individuals tended to have been engaged in less physically arduous occupations than control groups.

Race. The Hebrew race has been reported as having a significantly higher susceptibility to coronary occlusion than persons of other nationalities.[23] In a study of 5116 fatal cases of acute coronary occlusion in Philadelphia, Hedley[36] found the mortality from coronary disease among Russian Jews to be twice as high as among native-born white Americans. Perhaps this is related in some way to the well-known susceptibility of the Hebrew race to diabetes mellitus.

The Negro race has long been considered to have a much lower incidence of coronary disease than the white race.[44, 16] More recent reports have suggested only a moderately lower frequency among Negroes.[40, 105]

The infrequency of advanced coronary sclerosis and coronary occlusion among the Chinese has been discussed in the chapter on arteriosclerosis (p. 342).

Season. A number of observers have noted that attacks of acute coronary occlusion occur more frequently during the winter than during the summer months.[43] On the other hand, Master, Dack and Jaffe[60] observed no significant relationship between the seasons and the incidence of acute coronary occlusion.

Heredity. Hereditary susceptibility appears to be a more fundamental etiologic factor in the occurrence of coronary sclerosis and occlusion than most of those already mentioned. Every physician who has obtained a careful and accurate family history in his patients with coronary artery disease must have been impressed by the frequency with which angina pectoris, sudden death or proven attacks of acute coronary thrombosis occur in several members of the same family. I have found this family tendency to be most striking in patients who suffered their acute coronary occlusion at an early age. One of my patients died of his first coronary occlusion at the age of thirty-five and his only brother of the same cause at thirty-nine. Their father had died suddenly at forty and their paternal grandfather had also died suddenly in his early forties, both presumably of a heart attack. Hypertension, cerebral hemorrhage or thrombosis and diabetes mellitus appear to occur with more than average frequency in the same families.[38, 30, 6, 82] The hereditary factor in familial hypercholesterolemia and xanthomatosis and its relation to coronary occlusion has been noted (p. 959).

Body Build. There is very little scientific information regarding an association between specific types of body build and the occurrence of arteriosclerotic coronary occlusion. Obesity has been frequently mentioned as a predisposing factor.[2, 26] Yater et al.[105] found only a slight tendency for men with coronary disease to be overweight. It is of interest that obesity has also been invoked in the etiology of hypertension and diabetes, two conditions which have been mentioned as prominent factors predisposing to coronary occlusion.

Patients with acute coronary thrombosis have been described as conforming to a definite constitutional type characterized by a short, stocky stature, some obesity, a thick short neck and a barrel-shaped chest but this is unproven. Furthermore, constitution involves a multiplicity of intricate elements which would have to be analyzed carefully to determine which ones specifically were concerned with the occurrence of coronary thrombosis. For guidance in diagnosis it is more important to emphasize that coronary occlusion may occur in persons of any build, than to stress any special predisposing constitutional type.

Temperament. The rising incidence of acute coronary thrombosis has sometimes been attributed to the increased strain of modern living. Many patients with this disease disclose a history of recent or prolonged psychic conflict and emotional stress. For this reason, coronary thrombosis, like hypertension, peptic ulcer and hyperthyroidism, has been interpreted by some as primarily a psychosomatic disease occurring in specific susceptible personality types.[1] Many of the patients with advanced coronary disease may be described as aggressive, ambitious individuals with an intense physical and emotional drive, who have no hobbies and have not learned to play, and who have concentrated all their thoughts and energy in the narrow groove of their career.[46] It need hardly be mentioned that there are also patients with coronary occlusion who do not fit this description. The interpretation of this condition as primarily a psychosomatic disease has little scientific support at the present time. However, the possible importance of psychic factors in the etiology of coronary artery disease is worthy of careful investigation.

Tobacco and Alcohol. There is no significant evidence that excessive smoking or overindulgence in alcoholic drinks contributes to the development of advanced coronary artery disease or acute coronary occlusion. Smoking has been implicated (a) because it has been proved harmful in another vascular disease, thromboangiitis obliterans, (b) because of the vasoconstrictive effects of smoking on the peripheral circulation and (c) because in some patients it appears to precipitate attacks of angina pectoris (p. 359). Although there is insufficient evidence of significant causal relationship between smoking and advanced coronary sclerosis and occlusion, smoking may for other reasons have an unfavorable influence on longevity and may therefore justifiably be interdicted for the patient with severe coronary disease.

Alcohol, on the other hand, has long been viewed with favor as a therapeutic agent in patients with coronary sclerosis and angina pectoris, although its pharmacologic effect on the coronary circulation is uncertain. There is no definite evidence that the ingestion of alcohol either contributes to the development of coronary sclerosis or significantly affects its course for better or for worse once coronary arteriosclerosis and occlusion have occurred.

Precipitating Factors

We have seen that attacks of angina pectoris occur promptly after certain precipitating factors such as effort, exposure to cold, the intake of food and emotional excitement. Although an acute coronary occlusion also appears to develop suddenly, its precipitating factors are still unknown and the causes responsible for attacks of angina pectoris do not usually initiate a coronary occlusion. Analyses of the events immediately preceding episodes of acute coronary occlusion have not usually demonstrated a causal relationship between specific activities and the occlusion.

Physical Exertion. In a study of patients' activities immediately prior to an acute coronary occlusion in 437 cases, Phipps[77] noted physical exercise in only 13 per cent and moderate or usual exertion in 18 per cent, while in 51 per cent of the cases the patient was at rest and in 8 per cent asleep. Surgical procedures had been performed in 6 per cent. In 10 per cent of the cases the occlusion had occurred during moderate exertion after a heavy meal and in 12 per cent after a meal but with the patient at rest. Similar investigations by Master, Dack and Jaffe[60] revealed that among 1108 attacks of acute coronary

thrombosis, 52 per cent occurred while the patient was asleep or resting, 21 per cent during mild routine activity, 16 per cent while the patient was walking and 9 per cent during moderate activity. In only 2 per cent was there a history of unusual physical exertion. This analysis led the authors to conclude that the percentage of attacks which occurred during sleep, rest or mild, moderate or intense activity coincided with the proportion of the day spent in these states and that physical exertion, which is an important precipitating factor of angina pectoris, is not concerned in the initiation of acute coronary occlusion.

Unfortunately such studies may be invalidated by the difficulty of obtaining an accurate and complete history and especially by the nature of the pathology of coronary occlusion. Although the characteristic symptoms of acute coronary occlusion usually develop suddenly, the underlying pathologic process and functional disturbances associated with the occlusion may commence hours or days before distinctive symptoms appear. Sometimes there are premonitory symptoms during this period which are forgotten by the patient in the throes of the more intense symptoms of the full-blown attack. Not infrequently the patient denies any unusual effort prior to the occlusion, but questioning of a relative, friend or business associate discloses some extraordinary or dramatic activity which might have been causal. Since the actual occlusion precedes the striking symptoms of the attack by hours or days, the factors responsible for the occlusion may have acted hours, days or even weeks before the appearance of symptoms. Therefore efforts to discover the precipitating cause by recording the events or activities immediately preceding the first major symptom of an acute coronary occlusion may be misleading.

While the observations of Phipps[77] and of Master et al.[60] indicate that physical exertion is not a precipitating cause of acute coronary occlusion, other authors have reported cases in which there is strong circumstantial evidence for such a causal relationship. Among 100 cases of acute coronary occlusion, Fitzhugh and Hamilton[24] noted that the occlusion had occurred 24 times during or promptly following some unusual and violent physical exertion and 33 times after an unusual exertion which was not necessarily violent. Boas[12] reviewed reported cases of cardiac infarction following unusual effort and described briefly 13 out of 25 cases which had come under his personal observation. Cooksey[20] found that 17 out of 100 private cases of acute coronary occlusion had developed within twenty-four hours of definitely unusual and frequently extreme physical exertions. Smith and associates[91] found that physical exertion was associated with the attack in 32 of 53 cases of coronary occlusion. Yater and associates[105] reported that the proportion of attacks among young soldiers occurring during strenuous activity was more than twice as great as the proportion of time spent in such activity. French and Dock[26] found that 26 or 35 per cent of 80 fatal attacks of coronary disease occurred within one to several hours after vigorous exercise. The exertions reported as unusual or severe by these various authors included cranking a car in cold weather, lifting a heavy trunk, pushing a stalled auto, rowing, long hikes uphill, etc., all of which had never been performed previously by the patient in question or had not been done for many years. Fitzhugh and Hamilton[24] emphasized that the effort had often been performed when the subject was suffering from undue fatigue, inadequate sleep and excessive emotional strain. In conclusion, while the evidence adduced by Master and his

associates[60] might indicate that physical exertion is not an essential or even important precipitating cause in most cases of acute coronary thrombosis, it does not exclude the possibility that it induces at least some of the instances of coronary thrombosis.

Several suggestions have been offered to explain a possible causal relationship between physical exertion and acute coronary occlusion and myocardial infarction. The mechanism which most commonly initiates the actual occlusion is probably a capillary hemorrhage within an arteriosclerotic plaque in the intima.[76, 101, 103] Paterson[76] suggested that a rise in arterial blood pressure associated with physical exertion and emotion may be responsible for the rupture of intimal capillaries and a subsequent thrombosis. Physical exertion may also be indirectly related to the development of a myocardial infarct after an acute coronary occlusion has already occurred. Because of a collateral circulation, the occlusion itself may not produce sufficient myocardial anoxia to result in infarction. Severe physical effort at this time, by augmenting the work of the heart, may enhance the degree of anoxia and cause necrosis of myocardial tissue. This suggestion is supported by the finding of Yater and associates[105] that only 11 per cent of those patients with coronary artery thrombosis who died in bed had old or organizing thrombi while 38 per cent of those engaged in strenuous activity had such thrombi. Similarly the observation of French and Dock[26] that a fatal attack during exertion was often associated with severe coronary artery narrowing but no occlusion, may indicate that the exertion intensified a potential or relative coronary insufficiency to the point of causing fatal myocardial anoxia.

Emotional Strain. Emotional strain, even more than physical exertion, is difficult to evaluate as a factor in the occurrence of an acute coronary occlusion. The purported increase in the incidence of this condition has been loosely attributed to the stress of modern living. Clinical histories upon which such conclusions are based are usually incomplete or unreliable, for they are deficient in the necessary psychiatric detail. They often fail to include possible causative emotional disturbances which have occurred days or even weeks before the attack. The duration as well as the intensity of the emotional disturbance may be of etiologic importance. Emotional strains are varied in character and must be interpreted in terms of their effect on the individual and his reaction to them. In eliciting a history of emotional disturbance one must be certain that a similar history could not be obtained from numerous persons without a coronary occlusion or even from the patient himself during many previous years when he was perfectly well. But despite these difficulties and uncertainties, I do not wish to dismiss the possible relation of emotion to the precipitation of acute coronary occlusion without comment. I have so often noted the occurrence of this condition in persons who had been under an unusually severe and protracted emotional strain that I believe this possible relationship is worthy of serious study. Its implications in prophylaxis and therapy are obvious.

Coronary thrombosis has been observed after an acute emotional experience as well as after prolonged emotional stress. Boas[13] has reported some historical as well as personal cases of this type.

Trauma. Trauma may produce a pericardial and myocardial contusion with hemorrhage into and destruction of the muscle tissue of the heart (Chapter 44). The resulting clinical picture may resemble that of myocardial infarc-

tion. Or the injury may involve a large coronary artery and induce a coronary thrombosis with true myocardial infarction. The injury may be of the penetrating variety, such as a stab or gunshot wound, but similar consequences may result from nonpenetrating blows to the chest wall (p. 988).

These cases of traumatic myocardial contusion or of direct injury and thrombosis of a coronary artery must be distinguished from cases of arteriosclerotic coronary occlusion in which unusual physical exertion appears to be a possible precipitating factor. In the former, the essential causative role of the trauma may be supported by the finding at necropsy of a myocardial hemorrhage, or an injured and thrombosed artery in a heart whose vessels are otherwise normal. In the latter cases, the occlusion is found in a markedly arteriosclerotic vessel.

Operations. Attacks of acute myocardial infarction soon after operation have been observed with sufficient frequency to suggest that there is a significant causal relationship between the operation and the acute infarction.[87, 81, 64] Master and his associates[61] noted that at least 5.6 per cent of 625 attacks of coronary artery occlusion followed an operation. As a rule, the persons affected are beyond the age of fifty and usually past sixty. Pathologic observations have revealed that almost always there was preexisting severe coronary arteriosclerosis and often a previous coronary occlusion. The causal relationship to the operation appears to be supported by the occurrence of the infarction within a few days or at least within a week after the operation.

In most instances of acute myocardial infarction postoperatively, the infarction is secondary to an acute coronary occlusion on an arteriosclerotic basis. In other cases, however, the infarction occurs without associated coronary occlusion. The occurrence of shock with its associated fall in blood pressure could reduce the coronary blood flow and result in sufficiently severe myocardial anoxia to cause necrosis of muscle, even though the coronary vessels were not occluded (p. 422). This mechanism could be intensified by hemorrhage, dehydration and tachycardia. The possibility of a coronary occlusion after an operation often poses a problem in the diagnosis of postoperative complications, since the classic pain associated with myocardial infarction may be absent or overshadowed by other symptoms in these cases, and since postoperative myocardial infarction may closely resemble surgical shock and pulmonary embolism.

Among other factors[13] which have been reported as occasional precipitating or contributing causes of acute myocardial infarction are infections of the respiratory tract, insulin hypoglycemia,[29] artificial hyperpyrexia, high altitude, drinking of ice water, injections of antitoxin and so-called vascular allergy.

A history of angina pectoris has been noted in one third to two thirds of cases of acute myocardial infarction. This merely denotes that clinical evidence of advanced coronary arteriosclerosis or previous coronary occlusion often precedes a fresh coronary thrombus and cardiac infarct.

PATHOLOGIC PHYSIOLOGY

The Effect of Experimental Acute Coronary Artery Ligation

The early experimental attempts at acute ligation of a large coronary artery in animals usually resulted in rapid arrest of the heart and led to the conclusion that the coronary arteries were end arteries.[19] Porter[79] observed that

the frequency of cardiac arrest following experimental acute coronary occlusion in dogs was dependent in part on the type of anesthetic used. More recent observers have demonstrated that acute coronary occlusion in animals is not invariably fatal and is compatible with long periods of survival and well being.[92, 50]

However, if one of the three major coronary arteries is completely ligated close to its origin, a large infarct of the corresponding area of myocardium almost invariably develops.[92, 32] This corresponds in general with the usual consequence of a similar acute coronary occlusion in humans and suggests that functionally at least these vessels may act as end arteries, even though anatomical anastomoses exist and establish a functioning collateral circulation (p. 322). On the other hand, the acute experimental occlusion of a secondary branch or the acute occlusion of a major branch in its distal portion usually causes no infarct and no significant circulatory disturbance because under such circumstances the collateral circulation is capable of maintaining an adequate blood supply to the affected area of myocardium.

Myocardial Contraction after Acute Coronary Artery Ligation. In experimental animals, acute coronary occlusion has been seen to result in prompt disturbances in the area of heart muscle supplied by the occluded muscle even before anatomic necrosis developed. Orias[72] and Tennant and Wiggers[100] observed that this ischemic area became cyanotic immediately and myographic studies disclosed that the contractions of the affected muscle became weaker and that after one minute the muscle became stretched during systole, instead of shortening as it does normally. This abnormality in mode of contraction could be reversed if the clamp occluding the coronary artery was released within twenty minutes. Similarly, Blumgart and his associates[10] found that no structural damage to the heart muscle occurred following acute coronary artery ligation if the normal blood supply was reestablished after five to twenty minutes by removal of the occluding ligature; occlusion for more than twenty minutes produced focal areas of necrosis and fibrosis or massive infarction. These observations suggest that extreme myocardial anoxia results in irreversible muscular disturbance and necrosis only if prolonged beyond a minimum interval. Similarly in human cases of cardiac pain, which represent myocardial anoxia, persistence of pain for twenty minutes or more probably denotes that anatomic damage has occurred.

Electrocardiographic Changes after Experimental Coronary Artery Ligation. Concomitant with the disturbance in myocardial contraction following acute coronary artery ligation, the ischemic area undergoes abnormalities in electrical potential, as indicated by electrocardiographic studies.[92, 104, 35] Smith[92] reported serial changes in the T waves, ST segments and the initial deflection after experimental coronary occlusion in dogs. Bayley and La Due[4] observed that complete occlusion of a dog's coronary artery for ninety seconds produced immediate electrocardiographic changes in a unipolar lead over the affected myocardium. The resulting so-called ischemia-injury pattern[5] consists of a primary T wave inversion (ischemia) which is followed by RT segment elevation (injury) which disappears in less than a minute after releasing the occlusion. If the occlusion is maintained for longer periods, the more persistent serial changes of myocardial infarction appear.

Thermic and Chemical Changes. Following acute coronary artery ligation the affected ischemic area of myocardium also undergoes early thermic and

chemical changes even before there are visible anatomic alterations. Sutherland and Dial[97] noted a drop in temperature of 2° to 8° F. after the occlusion, but if the ligature on the coronary artery was released after a few minutes the temperature of the muscle rose promptly to its former level.

Ligation of a coronary artery in animals also results in an increase of the lactic acid and a decrease of the glycogen content of the muscle which has been deprived of its circulation.[39, 99] Reestablishment of the circulation for two hours was followed by a return of the lactic acid content to normal, but the glycogen level was not restored, indicating that the reduction in lactic acid was not due to its resynthesis into glycogen.

Lowry, Gilligan and Hastings[56] found characteristic increases in the water, sodium and chloride content of the myocardium after temporary coronary occlusion in dogs. There was no significant change in potassium concentration. These changes were interpreted as denoting an increase in the proportion of extracellular fluid without demonstrable change in the muscle fibers themselves.

Anatomic Changes Following Acute Coronary Artery Ligation. In contrast with the prompt electrical, thermal and chemical changes following experimental acute coronary artery occlusion, no histologic changes were observed by Tennant et al.[99] until eight hours after the ligation. After this interval, edema of the interstitial tissue and the deposition of fat droplets were noted; after twenty-eight hours necrosis and increased fatty deposits in the muscle fibers, and an infiltration of polymorphonuclear leukocytes and red blood cells in the interstitial tissue were observed; after forty-eight hours fibroblasts appeared. Healing became prominent after four days, and after four weeks the infarcted zone was replaced by a dense fibrous tissue scar. These alterations developed only if the ligature was maintained for two to eight hours; if the ligature was released after an interval of thirty minutes or less, there were no demonstrable histologic changes.

Mallory, White and Salcedo-Salgar[57] noted that the conversion of a small infarct into a scar occurred in two weeks, while large infarcts required five weeks for this healing process. Cardiac rupture occurred occasionally, usually in the second week after the experimental occlusion. These observations correspond in a general way with the pathologic changes in human coronary occlusion and form an experimental support for the clinical practice of keeping patients in bed for at least three weeks and preferably six weeks after the occurrence of an acute coronary occlusion. The advantages of rest for the healing of the infarct are supported also by the experimental observations of Sutton and Davis,[98] who found that if they exercised dogs within three days after the production of an acute coronary occlusion, a ventricular aneurysm developed at the site of the infarct. If the animals were rested for at least six days following the coronary artery ligation, the infarct was converted into a firm scar.

Disturbances in Rhythm and Circulatory Dynamics. Following acute experimental coronary occlusion, ectopic beats are observed frequently and ventricular fibrillation is a common cause of death in the animals that do not survive the procedure. Fibrillation is often preceded by ventricular tachycardia.

Gross, Schauer and Mendlowitz[34] have shown that the essential changes in circulatory dynamics following experimental acute coronary occlusion are an immediate diminution in the average cardiac output and a delay in the cyanide circulation time. Mendlowitz and his associates[65] interpreted the former as

indicating hypokinetic circulatory failure and the latter as left ventricular congestive failure. These observations correspond to two of the main clinical observations in human cases of acute coronary occlusion, namely, the occurrence of cardiac shock and of pulmonary congestion or edema secondary to failure of the left ventricle.

Experimental Chronic Coronary Artery Ligation

Although experimental acute coronary occlusion is followed by changes which resemble those in human cases, human acute coronary occlusion differs in that it is usually preceded by a more or less prolonged period of progressive coronary narrowing during which there is an opportunity for the development of a collateral circulation. Therefore, in order to simulate more closely conditions in the human disease, attempts have been made to produce a gradual coronary occlusion in animals.

Beck and Tichy[7] effected a gradual obturation of a large coronary artery by repeated pinching with metal clips. Robertson[85] occluded the major coronary arteries in succession by serial ligation during a period of months. Blum, Schauer and Calef[9] gradually narrowed a major coronary artery near its origin by progressive tightening of a modified Goldblatt clamp for a period of five weeks until there was complete occlusion. The latter experimenters noted that in a control series of 25 dogs which had survived an acute coronary occlusion, a large infarct developed in 24 animals and a small infarct in the remaining one. On the other hand, extensive myocardial necrosis was observed in only 4 out of 14 dogs in which they had occluded the same coronary artery gradually. They concluded that the collateral circulation developing during gradual coronary artery occlusion sufficed to prevent a large part of the myocardial damage which resulted when the same vessel was occluded suddenly. In similar experiments Burchell[17] produced chronic coronary occlusion in the three main coronary arteries by first constricting them with metal clips for three weeks to three months and then ligating the vessels. He also noted that the complete closure of a large coronary artery did not necessarily result in myocardial infarction if the occlusion was produced gradually.

These experimental observations correspond to the findings in cases of human coronary occlusion in which myocardial infarction is a frequent but not an invariable consequence. They indicate that with gradual coronary narrowing anastomotic vessels may provide a collateral circulation sufficient to prevent infarction even when the actual occlusion is complete and sudden. On the other hand, the frequency with which infarcts appear even after gradual coronary occlusion, attests to the imperfection of the collateral circulation in most instances.

Factors Determining the Occurrence of Infarcts after Acute Coronary Occlusion

A number of factors determine whether or not a myocardial infarct will result from an acute coronary occlusion which occurs after a period of gradual narrowing as in human cases of this condition.

(1) *The size of the occluded artery.* Occlusion of any one of the major coronary arteries, the left anterior descending, the left circumflex or the right coronary, is usually followed by a myocardial infarct; occlusion of any of the smaller branches rarely causes significant myocardial necrosis.

(2) *The site of occlusion.* The likelihood of myocardial infarction increases the nearer the site of occlusion is to the origin of a major coronary artery. The more distal the occlusion, the more vessels are available proximal to the occlusion to provide a collateral circulation.

(3) *The speed of occlusion.* Sudden complete occlusion in a normal large coronary artery is almost always followed by an infarct because an adequate collateral circulation has not been established. However, coronary embolism usually causes a prompt fatality before an infarct can develop. With progressive narrowing prior to occlusion as in coronary arteriosclerosis, the changes in pressure gradients in anastomotic vessels permit a gradual progressive increase in the relative blood flow through these collateral channels. When complete obstruction occurs, the myocardium affected may be receiving its major blood supply from these enlarged collateral vessels, and the occlusion of the original supplying vessel may not be of serious consequence.

(4) *The condition of the other major coronary arteries.* Myocardial infarction is less likely to follow an acute coronary occlusion if the other two major vessels are normal than if one or both are already occluded or extremely narrowed. Under the latter circumstances, the possibility that the remaining vessels will provide an adequate collateral circulation is less than if they were normal. In fact the first coronary artery occlusion often causes no infarction because an adjacent major artery provides sufficient blood to the affected area. This occlusion may, however, result in relative myocardial anoxia when the work of the heart is increased and may be manifested clinically by angina pectoris on effort. However, if the second major artery which provided the collateral circulation is then occluded, a myocardial infarct usually results because the first major artery supplying the area of myocardium is already closed.

(5) *The anatomic pattern of the coronary arteries.* The usual distribution of the coronary arteries and some of the variations have been described above (p. 321). Due to these variations occlusion of a given coronary artery may be of more serious consequence under some anatomic circumstances than under others.

Schlesinger[88] observed myocardial infarcts with the least frequency in the hearts with a balanced coronary circulation, next in those with a right coronary artery predominance and most frequently in those hearts in which there was a preponderant blood supply from the left coronary artery. Furthermore, in the left coronary preponderant group the first infarct was most likely to be fatal, while multiple infarcts (fresh and healed) were most common in the right preponderant group.

(6) *The effect of cardiac hypertrophy and other factors.* The deleterious effect of an acute coronary occlusion on the corresponding myocardial area may be intensified by associated diseases of the heart and circulation. If the heart is hypertrophied because of hypertension, rheumatic cardiovalvular disease, syphilitic aortic insufficiency, etc., there is a potential myocardial anoxia because of the increased need for blood due to the greater muscle mass and the augmented cardiac work. The slightly increased blood flow in hypertrophied hearts is relatively much less than the increased requirement. The acute obstruction of a major coronary artery is therefore more apt to produce myocardial infarction than in a normal-sized heart. In the presence of anemia, the probability of myocardial infarction following acute coronary occlusion may be similarly enhanced.

PATHOLOGY OF ARTERIOSCLEROTIC CORONARY ARTERY OCCLUSION AND CARDIAC INFARCTION

The Mechanism of Arteriosclerotic Coronary Occlusion

The pathology of coronary arteriosclerosis has been described (p. 343). Briefly the process consists of thickening of the intima by cellular hyperplasia and fibrosis, associated with the deposition of lipoid and fat. Newly formed capillaries appear in the thickened intimal plaque. Degenerative changes result in hyalinization and areas of softening (atheroma or atheromatous "abscess"), containing a gruel-like detritus of cells and lipoid material. Calcification of the arteriosclerotic intimal plaque occurs commonly and occasionally spicules of bone are formed. The atheromatous abscess may break into the lumen forming the atheromatous ulcer, the surface of which may be covered by thrombus. The artery becomes irregularly thickened and may be transformed into a more or less rigid tube. The thickening occurs at the expense of the arterial lumen which may become extremely stenosed.

It was formerly believed that occlusion of an arteriosclerotic coronary artery was due almost exclusively to obturation of the lumen by a thrombus deposited on an arteriosclerotic plaque or atheromatous ulcer. By recent studies[76, 101, 103] it was demonstrated that arteriosclerotic coronary occlusion may occur without thrombosis and that capillary hemorrhages into the arteriosclerotic intima are frequently important in the production of occlusion with or without thrombosis. In a study of 100 autopsied cases of acute arteriosclerotic coronary artery occlusion, Horn and Finkelstein[42] observed that the closure was due to intramural hemorrhage in 62.5 per cent and to formation of a thrombus on an arteriosclerotic plaque in 37.5 per cent of the cases.

One or more of the following mechanisms are now believed to be concerned in the occlusion of an arteriosclerotic coronary artery:

(1) *Intimal hemorrhage with rupture into the lumen and secondary thrombosis.* Due to the degenerative necrotic changes in the arteriosclerotic intima, the perivascular tissue no longer provides adequate support against the intracapillary pressure. Consequently the intimal capillaries often rupture and produce an intramural hemorrhage. According to Patterson,[76] changes in coronary arterial blood pressure (e. g., due to hypertension, physical and emotional stresses) may predispose to or precipitate intimal hemorrhage. Such hemorrhages may occur frequently, as part of the arteriosclerotic process, without necessarily leading to coronary occlusion. When there is extensive intimal degeneration associated with atheromatous abscess, even a small intimal capillary hemorrhage may rupture the arterial endothelium. A thrombus forms at the site of the endothelial tear and leads to occlusion of the arterial lumen. Occasionally the capillary hemorrhage does not itself rupture the arterial endothelium, but may by exaggerating the already extensive intimal degeneration initiate subendothelial and endothelial necrosis and consequent thrombosis. Often the relationship between the coronary thrombosis and the intramural hemorrhage can be recognized only by a study of serial sections of the artery in the neighborhood of the occlusion.

(2) *Intimal hemorrhage with occlusion by intramural hematoma.* Sometimes the arteriosclerotic process causes such thickening of the arterial wall that only a very small lumen remains. Rupture of an intimal capillary may result

in an intramural hematoma. The swelling thus induced may be sufficient to occlude completely the already narrowed arterial lumen, even without the occurrence of thrombosis.[101]

(3) *Coronary thrombosis on an arteriosclerotic intimal plaque.* In many cases of arteriosclerotic coronary thrombosis, the occlusion is not precipitated by intimal capillary hemorrhages. The intima may disclose merely dense fibrous thickening and lipoid infiltration or extensive necrosis and atheromatous ulcer. It is probable that the thrombosis is precipitated by arterial endothelial damage by direct impingement of the atheromatous abscess or by rupture of the abscess into the lumen or by other subendothelial degenerative changes. Leary[49] has emphasized the occurrence of coronary artery thrombosis at the site of atheromatous ulcers and Saphir and his associates[87] noted that in their 32 cases of coronary thrombosis the thrombi were located on atheromatous ulcers. In general the thrombosis occurs in the region of the most extensive arteriosclerotic change and at the point of greatest narrowing.

Pathology of Coronary Thrombi

Multiple coronary thrombi are found more often than a single thrombus. Many thrombi are overlooked because of failure to examine carefully all of the important branches of the coronary arteries throughout their entire extent. Occasionally a thrombus is expelled by the dissecting scissors. By making serial cross sections of the various coronary arteries with the scalpel, at intervals of 3 to 5 mm., Gross and I[33] observed multiple fresh and old coronary occlusions in about 85 per cent and a single coronary occlusion in only 15 per cent of 120 hearts with coronary occlusion. Saphir and his associates[87] noted more than one occlusion or extreme narrowing in every one of 34 hearts which they examined. Blumgart, Schlesinger and Davis,[11] in a study of hearts by a combined injection and dissection method, also found that more than one occlusion was usually present in the hearts showing advanced coronary arteriosclerosis, thrombosis or myocardial infarction.

Fresh and old coronary occlusions are usually found in the same heart. Fresh thrombi appear red and are soft and friable. They are loosely adherent to the arterial wall and easily dislodged. The thrombi undergo organization early. After twenty-four hours fibroblasts and capillaries appear.[8] Within a few days the red blood cells degenerate and are gradually absorbed and the fibrin is replaced by collagen. The thrombus during this period appears brownish and is more firmly attached. Eventually it undergoes complete fibrous replacement and the pigment disappears. The thrombus becomes firm and gray and is securely attached to the wall of the artery. Recanalization of the lumen occurs commonly and may lead to a partial but inadequate reestablishment of the circulation. Frequently it is impossible to determine with certainty whether we are dealing with an old recanalized thrombotic occlusion or with extreme arteriosclerotic narrowing or obliteration of the lumen, for vascular channel formation in an arteriosclerotic plaque may closely simulate recanalization of an old, healed thrombus.

Localization of Coronary Artery Occlusions

It was formerly believed that occlusion occurred predominantly in the anterior descending branch of the left coronary artery. Levine and Brown[51] noted occlusion of the left anterior descending branch 39 times, and of the right

coronary artery only twice in their 46 cases of fatal coronary thrombosis. More recent studies have disclosed that coronary occlusion occurs with almost equal frequency in the left anterior descending and the right circumflex arteries, while occlusion of the left circumflex coronary artery develops somewhat less often. In addition, occlusions are found not infrequently in somewhat smaller branches such as the ramus primus of the left anterior descending and in the branch to the obtuse margin of the heart which arises from the left circumflex. In 100 autopsied cases of acute coronary artery occlusion Horn and Finkelstein[42] observed 61 occlusions of the right coronary artery (right circumflex), 56 in the left anterior descending, 27 in the left circumflex, 15 in the ramus primus and 7 in the branch to the obtuse margin.

In my experience, occlusions are found most commonly in the proximal portions of the affected vessels, but rarely in the first two centimeters. The former belief that the region from 2 to 3 cm. from the origin of the left anterior descending artery was a site of special predilection for coronary thrombosis has not been substantiated by more recent careful studies. Blumgart and his associates[11] described a great variety of localization of the occlusions within each of the major arteries. The relative freedom from occlusion of the proximal 2 cm. of the vessels is of particular importance because it permits a free circulation through the first branch or two proximal to the occlusion, by means of which a collateral circulation may be maintained. This explains the possibility of survival of humans and experimental animals even after multiple occlusions involving both coronary arteries.

Occurrence and Location of Cardiac Infarction

The occlusion of one major coronary artery may not be followed by cardiac infarction either because death ensues too rapidly, i. e., within a period of minutes or a few hours, or because the flow of blood through collateral channels maintains the viability of the affected myocardium. The former circumstance is noted chiefly in cases studied by coroners. Thus Benson[8] observed 54 instances of recent coronary thrombosis without infarction among 1750 autopsies in the Portland morgue. Usually myocardial infarction follows the recent occlusion of two major coronary arteries, or it results from one recent occlusion in the presence of at least one old occlusion or the extreme narrowing of one or more large branches. However, myocardial infarction may follow the first acute coronary thrombosis, provided death does not result within the first few hours thereafter.

In most cases the infarct lies within the area of myocardium supplied by the recently occluded vessel. The extent of the infarct varies considerably from laminar patches 1 to 2 cm. in diameter to widespread areas of necrosis which extend through and through from the endocardium to the pericardium. *Occlusion of the left anterior descending artery* often causes infarction of the anterior wall of the left ventricle near the apex, but more extensive areas of the anterior wall of the left ventricle, of the papillary muscles, and of the anterior portion of the septum may be involved. *Occlusion of the left circumflex artery* usually produces infarction of some portion of the lateral wall of the left ventricle or of the posterior wall near the base. *Occlusion of the right circumflex artery* usually results in an infarct of the posterior wall of the left ventricle near the base and it may include a variable portion of the posterior half of the interventricular septum. The septum has such a rich anastomotic

circulation that it is rarely infarcted to any great extent unless both major vessels are occluded or unless one is severely narrowed and the other occluded. Infarction of the region of the auriculoventricular node usually is due to occlusion of the right coronary artery close to its origin.

The location and extent of the infarct depend not only on the size and location of the vessel recently occluded but also on the presence or absence of other occlusions, recent or old, on the degree of narrowing of unoccluded vessels, on the volume of the collateral circulation in adjacent vessels, on the anatomic pattern of the coronary vessels, as well as on other factors. These variables account for the frequent lack of correspondence between the site of infarction and the area normally supplied by the occluded artery. Thus an initial occlusion of the obtuse marginal branch of the left circumflex artery may produce no infarct of the posterolateral wall of the left ventricle which it supplies because this region may continue to receive an adequate blood supply from collateral branches of the right circumflex. A subsequent acute occlusion of the right circumflex, by eliminating this collateral circulation, may produce infarction of the area formerly supplied by the now occluded left circumflex branch, while the posterior wall of the left ventricle supplied by the right circumflex maintains its viability through collaterals from the main left circumflex.

Cardiac infarction is confined almost exclusively to some portion of the left ventricle or the interventricular septum. The right ventricle is involved rarely; Saphir and his associates[87] observed one instance of right ventricular infarction in their 34 cases of myocardial infarction, and Wartman and Hellerstein[102] 4 in 160 cases. Whether this is due to a richer coronary anastomosis,[80] to the relatively smaller myocardial mass of the right ventricle or to other factors is unknown. Occasionally infarction of the atria results from arteriosclerotic coronary artery occlusion simultaneously with ventricular infarction. Atrial infarcts, usually involving the right atrial appendage, were reported in 17 per cent of cases of ventricular infarction.[55] I have also seen atrial infarction in a case of periarteritis nodosa with coronary thrombosis. Within the wall of the left ventricle the site most frequently and most severely affected is the subendocardium. The papillary muscles are also frequently involved. The intermuscular branches of the coronary arteries extend perpendicularly from the main, superficial vessels in the epicardium and terminate in the subendocardium. The latter represents the periphery of the coronary circulation and therefore suffers most intensely from a reduction in the coronary blood flow. The endocardium itself is adequately nourished by the blood within the cardiac lumen. In cases of patchy necrosis or infarction due to coronary insufficiency without coronary occlusion, the lesions are confined to the subendocardium and papillary muscles.

The localization of myocardial infarction according to muscle bundles has been described by Robb and Robb.[84]

Macroscopic and Microscopic Pathology of Cardiac Infarcts

The earliest changes of infarction of the myocardium are those of ischemic or coagulation necrosis. The affected heart muscle appears pale, yellowish or gray. Its consistency becomes firmer and drier than that of the surrounding muscle. The periphery of the infarct is often delineated by a more or less regular reddish zone of hyperemia. *Microscopically,* at this early stage the muscle fibers

are seen to have lost their nuclear structure while the nuclei of the connective tissue and blood vessels are still apparent. But soon, especially in large infarcts, the cells of the connective tissue and blood vessel walls also undergo necrosis. At an early stage the muscle cells show evidences of hyaline and granular degeneration and loss of myostriation. These changes are associated with an uneven staining of the muscle fibers resulting in the appearance of deeper and lighter eosinophilic bands.

Somewhat later there is complete necrosis of the cells of the connective tissue and blood vessels as well as of the muscle fibers. The muscle fibers become completely vacuolized and eventually there is complete homogenization or disappearance of many muscle fibers. Hyperemia of the surrounding vessels and the accumulation of polymorphonuclear leukocytes, lymphocytes and mesenchymal cells are evidences of reaction to the necrotic cardiac muscle. The polymorphonuclear leukocytes may invade the necrotic muscle and produce an appearance somewhat similar to that of an acute suppurative inflammation. Between the central zone of necrosis and the peripheral zone of hyperemia there may be a yellowish band of fatty infiltration due to partial anoxia. Often there is an extravasation of red blood cells from the congested vessels and the entire area of infarction may appear hemorrhagic. The infarct appears yellowish, green or gray, often mottled or streaked with hemorrhage, depending on the predominance of one or the other of these changes.

The infarcted muscle undergoes various degrees of friability or softening (*myomalacia*) due to the transudation of fluid from the neighboring vessels into the degenerated muscle tissue. If the degree of softening is extreme, the infarcted muscle may become the site of a small irregular tear, resulting in *cardiac rupture* (p. 456). Complete rupture, usually in the anterior wall near the apex or the posterior wall at the base of the left ventricle, is followed by hemorrhage into the pericardiac sac (*hemopericardium*) and a fatal issue. Occasionally extreme softening of an infarct produces a *rupture of the interventricular septum* which may be diagnosed intra vitam and which is usually but not always fatal (p. 457). Rupture of a papillary muscle is also a rare complication of myocardial infarction (p. 457). Cardiac rupture may be incomplete and the seepage of blood through the tear produces a dissecting aneurysm of the heart, which may appear as an hemispherical bulge of the cardiac surface. A considerable interval may elapse between the development of an incomplete cardiac tear and dissecting aneurysm and the occurrence of a complete rupture.

Organization of a myocardial infarct begins within a week. The necrotic material is resorbed and the infarcted area is invaded by a granulation tissue rich in blood vessels and fibroblasts. Remnants of necrotic muscle are still visible within the granulation tissue. Pigment granules giving a positive iron reaction are seen within and outside macrophages and are residua of old hemorrhage. At this stage of early organization the hemorrhagic infarct is converted into a grayish red area of healing. Eventually the granulation tissue is replaced by a dense collagenous tissue rich in elastic fibers which is converted into an avascular scar. Grossly this appears as a pearly white tendon-like cicatrix of varying extent. Occasionally the healed infarct becomes more or less calcified[89] and rarely bone may be formed.[18] Fresh and old infarcts are often observed in the same heart.

Cardiac aneurysms are not infrequently associated with both fresh and old

infarcts (p. 458). An aneurysm at the site of a fresh myocardial infarct is often overlooked unless the affected ventricle is distended with fluid under pressure. Where an infarct heals, the damaged myocardium may become thinned and stretched into an aneurysm. At postmortem examination the aneurysm may appear as a pale depressed area or as a localized bulge.

Endocardial and Pericardial Lesions in Cardiac Infarcts

Cardiac infarcts frequently damage or rupture the endocardial endothelium either by direct involvement of the entire endocardial thickness or by an hemorrhagic extravasation which produces a dissecting aneurysm extending to the cardiac lumen. An endocardial thrombus very often overlies fresh or healed infarcts. Mural thrombi were found at autopsy in 44 per cent of 924 cases of acute myocardial infarction reported by various observers.[37] These mural thrombi are almost always situated in the left ventricle, especially at the apex. But when there is extensive infarction of the interventricular septum, mural thrombi may develop on both sides of the septum. Occasionally large semispherical masses of thrombi fill the cavity of a bulging aneurysm at the apex of the left ventricle. While these thrombi are quite adherent to the endocardial surface, superficial portions may become detached and cause embolization of the brain, the viscera or the extremities. However, pulmonary emboli, which commonly complicate acute coronary occlusion, arise usually from thrombi in the veins of the lower extremities and only occasionally from mural thrombi in the right ventricle.

Cardiac infarcts extend frequently also to the pericardial surface and produce a localized, or occasionally an extensive fibrinous pericarditis.[96] With recent infarcts, there is a dull fibrinous exudate overlying the area of necrosis, while healed infarcts are covered with a gray or white adherent patch of scar tissue. Pericarditis was observed at autopsy in 28 per cent of 111 cases of myocardial infarction analyzed by Wartman and Hellerstein.[102] Effusions develop occasionally when a wide area of pericardium is involved.[90, 71]

Size of the Heart after Cardiac Infarction

Cardiac enlargement or hypertrophy occurs in at least two thirds of the cases of cardiac infarction due to coronary artery occlusion. Palmer[73] observed cardiac enlargement, as determined roentgenologically, in 128 (64 per cent) of 200 clinical cases of coronary thrombosis, and Bartels and Smith[3] noted cardiac hypertrophy in 37 (88 per cent) of 42 infarcted hearts examined postmortem.

However, it is uncertain whether or how frequently cardiac hypertrophy is the direct consequence of the cardiac infarct or whether it is always due to associated conditions or to complications of the infarct. Hypertension is present in the great majority of patients with coronary artery occlusion and may represent the commonest cause of cardiac hypertrophy in such cases. The etiologic role of hypertension may be overlooked because the blood pressure often falls to within the normal range after an attack of coronary artery occlusion. In other cases an associated rheumatic cardiovalvular disease or syphilitic aortic insufficiency may account for the enlargement of the heart.

But cardiac hypertrophy undoubtedly occurs in cases of coronary artery occlusion in the absence of such associated conditions. In such cases the hypertrophy has been interpreted as a direct consequence of the ischemia due to the

coronary artery occlusion. This conclusion is based on evidence that cardiac hypertrophy may follow experimentally induced anemia and that it occurs in various clinical forms of anemia (p. 970) and in cases of an anomalous coronary artery arising from a coronary sinus and supplying the heart with relatively unoxygenated blood (p. 679). More direct evidence was adduced by Smith, Miller and Graber,[93] who observed the development of cardiac hypertrophy in dogs following experimental coronary artery ligation. Unlike these observers, Sutton and Davis[98] saw no change in the size of the heart in dogs following coronary artery ligation.

My own observations have led me to believe that when cardiac hypertrophy follows coronary occlusion it is due either to present or preexistent hypertension, to associated cardiovalvular disease, or to congestive heart failure caused by severe extensive myocardial damage. Sohval and I[28] studied the hearts at autopsy of 100 cases of acute coronary occlusion to determine the relationship of this condition to cardiac hypertrophy. Hearts with associated cardiac disease had been excluded. The cases with and without hypertension were segregated. Evidence of previous hypertension in patients with normal blood pressure during their final illness was sought in the records of previous hospital admissions or from their family physicians. Preexistent hypertension was also assumed to have been present if the examination of the fundus had disclosed severe arteriosclerosis and if postmortem examination disclosed advanced arteriosclerosis of the interlobular arteries or arteriolarsclerosis. The presence or absence of cardiac hypertrophy was based on the relationship of the heart weight to normal body weight and comparison of this figure with the normal figures of Smith.[94] This study disclosed that cardiac hypertrophy was absent in every case of acute coronary occlusion without evidence of hypertension or associated cardiovalvular disease, unless there were distinct clinical or pathologic signs of congestive heart failure. In the presence of congestive heart failure, marked cardiac hypertrophy was noted whether or not there was associated hypertension. Within the hypertensive group, cardiac hypertrophy was much more prominent when the hypertension was associated with failure than in the absence of failure. Hypertension per se was accompanied by lesser degrees of hypertrophy than heart failure without hypertension.

Davis and Blumgart[21] also noted the relationship of congestive heart failure to the occurrence of cardiac hypertrophy in a study of cases of heart failure not due to hypertension, valvular disease or other accepted causes of hypertrophy. In 14 of 15 cases of congestive heart failure associated with advanced coronary arteriosclerosis, the heart weights were above 400 gm., and in 11 of these above 500 gm., and in 5 above 600 gm. On the other hand, in 31 cases of advanced coronary heart disease without associated heart failure only 6 hearts weighed more than 400 gm. and no heart weight exceeded 440 gm. Davis and Blumgart[21] concluded that the failure was the cause and not the result of the cardiac hypertrophy, since otherwise they would have found some markedly hypertrophied hearts which had not yet failed.

Although cardiac hypertrophy is seen pathologically and cardiac enlargement is observed clinically in many cases of coronary occlusion, it is important to emphasize that the heart is often of normal size in this condition. Horine and Weiss[41] reported 20 cases of acute coronary thrombosis followed roentgenologically for periods between five months and ten years, in all of which the size of the heart was normal during the entire period of observation. Miller

and Weiss[66] studied 19 necropsied hearts with old cardiac infarcts, none of which disclosed cardiac hypertrophy. In a roentgenographic study of 200 patients with acute coronary thrombosis followed for an average period of three years, Palmer[73] found 72 (36 per cent) to be of normal size. Of those which were enlarged, only 4 (2 per cent of the total series) were not associated with hypertension or other conditions which are accepted as causes of cardiac enlargement. No mention was made of the possible role of congestive heart failure in these cases. In a somewhat similar roentgenologic study of the hearts of 16 patients with acute coronary thrombosis, Massie and Miller[58] noted no change whatever in the size or shape of the heart in 8 cases. In the first two weeks following the acute attack, an increase in heart size was observed in only 2 cases. The absence of cardiac enlargement should therefore not depreciate a clinical diagnosis of acute coronary occlusion. The presence of cardiac enlargement should merely suggest associated or complicating conditions.

RECENT MYOCARDIAL INFARCTION WITHOUT ACUTE CORONARY OCCLUSION

Experimental and pathologic observations have revealed that coronary artery occlusion is not invariably followed by cardiac infarction, because of the presence or development of collateral circulation. It is less well known that areas of acute myocardial necrosis or infarction occur frequently in the absence of a recent occlusion of a coronary artery. Isolated observations of this kind were noted by Libman,[54] Saphir et al.,[87] Büchner et al.,[15] among others. Friedberg and Horn[27] found that in a series of 1000 consecutive autopsies 31 per cent of the cases of acute myocardial infarction were not associated with a recent coronary artery occlusion. All the coronary vessels were meticulously examined by transverse sections of the arteries at intervals of 3 mm. and microscopic examinations were made of all extremely narrowed portions of the vessels. In 37 such cases of acute myocardial infarction without recent coronary occlusion, pulmonary embolism was associated in 12, calcific aortic valvular stenosis in 8, severe coronary and old occlusions with congestive heart failure in 6, an operative procedure in 4, a severe, acute anemia in 3, malignant hypertension and a cerebral complication in 3 and occlusion of the superior mesenteric artery in 1.

It is probable that myocardial infarction may occur whenever there is prolonged, severe myocardial anoxia, whether this be due to a mechanical occlusion or to other disturbances in circulatory dynamics which result in coronary insufficiency. In the above cases of myocardial necrosis or infarction without recent coronary occlusion, there were many factors which could result in a sharp inadequacy of the coronary blood supply for the needs of the myocardium. Shock following operation or mesenteric thrombosis, the fall in aortic and therefore in coronary blood pressure after a massive pulmonary embolism or acute hemorrhage could precipitate such a coronary insufficiency. In cases of calcific aortic stenosis there is a progressive increase in intraventricular pressure with a diminished cardiac output and a deficient filling of the coronary capillaries (p. 607). At the same time there is a greatly augmented need for blood because of cardiac hypertrophy and the increased work of the heart with this valvular lesion. In most of the cases a severe narrowing of the coronary arteries or an old occlusion had already impaired the coronary circulatory reserve.

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20

ACUTE CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

Clinical Features

SYMPTOMATOLOGY

Premonitory Symptoms

Usually acute myocardial infarction presents itself as a sudden catastrophic incident, and its definitive clinical picture develops without warning prodromata. But numerous recent studies[53, 139, 21, 103, 27, 167] disclose that preliminary chest pain may represent an harbinger of acute coronary occlusion in 10 to 50 per cent of the cases. Such premonitory pain usually develops within twenty-four hours prior to the occlusion, but it may precede the attack by several days or even weeks. Occasionally palpitation, weakness or dizziness may represent the premonitory symptoms, with or without associated pain.

The premonitory pain is usually identical with that of angina pectoris in character and location and in being often precipitated by exertion or emotional excitement. Of course, such pain can be considered definitely a premonitory symptom only if the patient has not been subject to regular attacks of angina pectoris for many months or years, and if it is followed by the more definitive clinical picture of acute cardiac infarction within a few days or at most a few weeks. The absence of characteristic electrocardiographic changes and other objective evidence of myocardial infarction during the interval substantiates the concept that the pain is actually a preliminary symptom and not due to the infarction itself.

Some authors, e. g., Blumenthal and Reisinger,[21] attach significance to the preliminary anginal pain when it occurs without apparent precipitating cause, when it is of longer duration than the usual paroxysm of angina pectoris and when it is not relieved by rest. In my own experience the most striking instances of premonitory pain have been observed in patients with previous myocardial infarcts and usually with angina pectoris on effort. In these patients a fresh coronary occlusion and cardiac infarct were often signalized by increasing frequency and severity of the episodes of angina pectoris which appeared with less and less exertion and even at rest.

The pathologic basis for the premonitory pain may be a sudden narrowing of a coronary artery due to the rupture of intramural capillaries in an arterio-

sclerotic plaque. The interval preceding the actual infarction represents the time required for the formation of a thrombus or hematoma sufficient to occlude the artery completely. It is also possible that the sudden appearance of premonitory angina pectoris actually corresponds to a coronary occlusion but that infarction of the heart muscle is delayed until exertion or some other factor, by enhancing the oxygen requirement of the ischemic area of heart muscle, intensifies the myocardial anoxia and produces necrosis.

Recognition of these premonitory symptoms has been stressed because an early diagnosis of impending coronary occlusion may prompt immediate institution of rest in bed and other therapeutic measures. Whether such measures would actually diminish the mortality rate or the frequency of complications is unknown. However, since myocardial infarction does not invariably follow coronary occlusion, immediate rest in bed by diminishing the work and oxygen requirement of the heart muscle might occasionally inhibit the development of myocardial infarction despite the coronary occlusion.

Desirable as these theoretical benefits might be, in practice it is difficult to evaluate this preliminary pain except in retrospect after the full picture of myocardial infarction has unfolded. Quite frequently identical pain and associated symptoms are later found to represent episodes of angina pectoris which are not followed by myocardial infarction. On the other hand it is important to recognize that many episodes of anginal pain or so-called premonitory pain actually represent attacks of myocardial infarction even when the classic symptoms of the latter are absent. Such symptoms may be properly interpreted only when careful studies are made of the temperature, white blood count, sedimentation time and electrocardiograms.

Clinical Picture of Acute Myocardial Infarction

For purposes of presentation, the clinical picture of acute myocardial infarction may be classified according to the following distinctive features:

1. Cases dominated by pain.
2. Cases dominated by shock.
3. Cases dominated by pulmonary edema or other evidence of acute left ventricular failure.
4. Cases characterized by the more gradual development or aggravation of congestive heart failure.
5. Cases dominated by complications.

Emphatically I do not intend to pose these groups as distinct entities; most cases are characterized by a combination of the symptoms and signs listed under the various headings. However, one group of symptoms or the other often dominates the clinical picture and recognition of acute myocardial infarction will be facilitated by a knowledge of these varied and sometimes sharply different clinical forms that the disease may assume.

1. Cases Dominated by Pain. In its most characteristic form the clinical picture of acute coronary occlusion with myocardial infarction is dominated by severe and prolonged pain in the region of the sternum, the precordium or the upper abdomen.[75, 93, 169, 66, 72, 89] The victim is stricken while at rest or at work, when awake or asleep, with or without the dubious benefit of premonitory pain. The pain may either begin as a relatively mild but persistent discomfort which becomes increasingly severe, or it may strike with sudden terrifying in-

tensity. Often the subject has previously experienced paroxysms of angina pectoris. But despite certain similarities of the pain of myocardial infarction to that of angina pectoris, he often knows that this is a new and different pain. The pain may appear distinctive because for the first time it attacks while he is asleep or at rest, and without apparent cause. Or if it arises during walking or other exertion, it fails to subside promptly with rest. If the patient follows his custom of taking nitroglycerin to dispel his anginal pain, he discovers with alarm that this pain is not similarly alleviated.

Character of the Pain. The pain of acute myocardial infarction has the same quality of constriction, oppression or compression which characterizes angina pectoris, and it may be no more severe. But often it is more crushing in intensity and becomes intolerable because of its prolonged duration. Usually the pain is characterized as squeezing, constricting, choking, vise-like or like a heavy weight, but it has also been described as expanding, stabbing, knife-like, dull and boring, or burning in quality.

Location and Radiation. Almost always the pain is located in the retrosternal area. Often it spreads to both sides of the anterior chest, especially to the left. A prominent component of the pain may affect the epigastrium or upper abdomen. This accounts, in part, for the resemblance of myocardial infarction to acute surgical or chronic diseases of the abdominal viscera and for the frequency with which such cases were formerly diagnosed as acute indigestion.

Like the pain of angina pectoris, that of acute myocardial infarction radiates frequently to the shoulders and both upper extremities, to the neck and jaw, and to the interscapular region. Radiation of the pain to the neck is often described as causing a clutching or choking sensation. The pain in the upper extremities, more often in the left, may either extend continuously from the shoulder to the fingers, or reach only to the arms, or skip directly to the forearms or wrist. There may be only a dull ache, weakness or numbness of the wrists associated with severe substernal and precordial pain.

Duration of Pain. The pain persists in varying degree for many hours, occasionally for several days.

The duration of the pain is abbreviated frequently by the administration of morphine or some other opiate, but even opiates may hardly diminish the pain or at best leave a persistent dull ache or pressure. With or without morphine, the pain may not be constant even though prolonged. After an hour or two of severe pain, the pain may lessen perceptibly or subside entirely only to recur for hours or days in irregular rhythm.

In some cases there is intense pain for thirty minutes to one or two hours; thereafter the pain disappears completely and the patient may feel and appear perfectly well. Only electrocardiographic studies may disclose that the pain was due to an acute myocardial infarction. When a pericardial rub discloses the existence of an acute fibrinous pericarditis, there is usually no distinct change in the pain; occasionally, however, a recurrence or intensification of pain suggests a relationship to the pericardial lesion.

After the pain due to the myocardial infarct subsides, the patient may become subject to paroxysms of angina pectoris whether or not he suffered angina pectoris prior to the acute attack. These may occur while he is still in bed, as a result of slight activity, meals or emotional states. More often angina pectoris develops only during convalescence, upon the resumption of activities

out of bed. On the other hand, patients previously plagued by frequent attacks of angina pectoris may be completely relieved of their pain after they recover from the acute myocardial infarction.

Pathogenesis of the Pain of Myocardial Infarction. The essential similarities in quality, location and radiation support the theory that the pain of myocardial infarction, like that of angina pectoris, is due to myocardial anoxia (p. 368). Their differences may be satisfactorily explained without impairing this theory. In angina pectoris the pain is brief and paroxysmal because the myocardial anoxia is provoked only by certain activities or emotional states which are themselves transient. The pain subsides with the cessation of the causative factor or after administration of a vasodilator like nitroglycerin, because the myocardial anoxia is reversible and there is no significant permanent anatomic change. In cases of myocardial infarction the pain is prolonged because myocardial anoxia is usually due to mechanical occlusion of a coronary artery which is not transient or reversible; the artery is not capable of dilatation by nitrites. In cases of myocardial infarction without coronary artery occlusion the causative factors produce a severe and prolonged myocardial anoxia, sufficient to cause permanent myocardial damage.

The greater severity of pain of myocardial infarction as compared to that of angina pectoris is probably an expression of more extensive or more intense myocardial anoxia, and of the longer duration. The severity and persistence of the pain of myocardial infarction may be simulated during a paroxysm of angina pectoris caused by rapid walking if the patient forces continuation of his activity despite the pain. The extension of the pain of myocardial infarction to the upper abdomen may represent an overflow of pain impulses to a wider area of neighboring segments of the spinal cord, due to the severity and extent of the cardiac lesion. However, occasionally this localization may be due to an associated acute pericarditis, or perhaps occasionally to hepatic engorgement. Aside from these considerations, individual differences in pain sensitivity[94] and in the pathways of conduction of pain from the heart (p. 372) probably account for some of the variations in the severity, location and radiation of the pain of myocardial infarction.

The eventual course of the pain is determined by the pathologic and physiologic changes in the ischemic area. A variable central portion of the affected muscle undergoes complete necrosis and is no longer capable of causing pain, for the pain stems from anoxic but viable tissue. The peripheral rim of ischemic muscle, remaining viable, may receive a completely adequate collateral blood supply from anastomotic vessels. In that circumstance there may be no pain at all after the acute infarction, even with exertion. If the collateral supply is merely adequate to maintain viability but provides no reserve, this portion of the ischemic myocardium may become anoxic with effort or under other conditions which temporarily increase the oxygen need of the myocardium or diminish its blood supply. Then paroxysms of angina pectoris may follow recovery from the acute infarction.

Myocardial infarction without pain has been documented in a number of cases.[47, 82, 67, 127] There was no history of pain in 21 of 53 autopsied cases of coronary thrombosis analyzed by Davis.[37] In Bean's series[14] of 125 cases of acute myocardial infarction, pain was noted in only 75 per cent. Cases without pain have been described as "silent or atypical."[161] But usually these are characterized by the sudden development of pulmonary edema, congestive

heart failure, shock or weakness, features now recognized as intrinsic elements in the symptomatology of acute myocardial infarction. Pain is said to be uncommon with acute myocardial infarction occurring in Negroes, in whom dyspnea is the usual clinical manifestation.[76]

In many purported instances of acute myocardial infarction without pain I have been able to elicit a history of typical pain on requestioning the patient. Often pain was not reported by the patient because it was overshadowed by dyspnea, weakness or other symptoms. Some patients who deny the presence of pain will admit that they experienced a clutching or gripping sensation, a sense of strangulation or a feeling of a massive weight on their chests. Pain may also be overlooked when it is relatively mild and of brief duration, or forgotten if the diagnosis is made long afterward by electrocardiographic examination. If those instances are omitted in which pain is overshadowed by other symptoms, misinterpreted or forgotten, only a small percentage of cases of acute myocardial infarction remain which were unaccompanied by cardiac pain. Recent reports indicate that pain is absent in not more than 3 to 4 per cent of cases of acute myocardial infarction,[82, 127, 87] and Babey[5] could find only one case without pain in a series of 116. In some of these painless cases, coronary occlusion may have been followed by such prompt and complete ischemia of a portion of the myocardium that no pain could arise. This is apt to occur when a previous occlusion has produced myocardial anoxia without infarction and the fresh occlusion leaves this portion of anoxic myocardium without any collateral blood supply. Extreme shock following myocardial infarction may completely benumb the cerebral centers to the awareness of pain. Finally, hyposensitive individuals may experience no pain at all, atypical radiation of pain or substitution symptoms instead of pain. The latter include weakness, dizziness, syncope, sweating or vomiting instead of the usual and characteristic pain.[28] As most of these "substitution symptoms" are manifestations of shock, there may be some question whether pain is absent because of the hyposensitivity of the patient or because it is overshadowed by manifestations of shock.

2. Cases Dominated by Evidence of Shock. While some evidence of shock is often observed in the previous group of cases characterized by intense substernal pain, there is a group in which the manifestations of acute cardiac infarction are *primarily* those of shock. The patient suddenly experiences weakness which slowly or rapidly may develop into intense prostration or collapse. He may unexpectedly slump in his chair if sitting or fall to the ground if standing or walking. He may lose consciousness for a brief period, probably because of cerebral ischemia due to the low cardiac output. Syncope marked the onset of acute cardiac infarction in 10 of 200 cases studied by Cookson.[33] In extreme cases, shock may be followed by sudden death.

In milder cases, the patient may complain only of feeling weak, dizzy, faint or nauseated, or less specifically of feeling "sick." These symptoms may be very transient and associated with a cold sweat. Sometimes there is a terrifying, inexplicable fear of impending doom, "angor animi," out of proportion to the symptoms. Vomiting is not uncommon, and rarely diarrhea occurs. The patient may complain of thirst.

In instances of profound shock, the subjective symptoms are associated with cold clammy extremities and tip of the nose, a rapid, weak or thready pulse, pallor or grayish cyanosis and a low blood pressure and pulse pressure. In

attacks beginning with syncope, there is often a bradycardia, but there may be a tachycardia.[33] Respiration may be rapid and shallow, especially if there is some associated left ventricular (congestive) failure, and sometimes there is frequent sighing. The facial expression is often drawn and anxious. The patient's intellect may be clear, but often he is mentally befogged and apathetic. The oral temperature may be subnormal, while the rectal temperature is elevated. There may be a notable diminution in the urinary output and rarely complete anuria for twenty-four hours.[131]

When shock occurs, it usually evolves soon after the onset of myocardial infarction and lasts a few hours to one or two days. In fatal cases it may persist longer and until the patient succumbs. Often in such cases shock is accompanied by pulmonary edema. If the patient recovers from the shock state, some degree of weakness often persists. The patient may first become aware of other symptoms, hitherto obscured. He may complain of a pressure pain over the sternum or precordium, pain or weakness in the arms or forearms or numbness in the wrist or fingers. Epigastric fullness, gaseous eructations and other symptoms of indigestion may become annoying. Sometimes subsidence of shock may be followed gradually by the emergence of signs of congestive heart failure. In some cases shock may persist for one or two weeks, especially when there is extensive or progressive myocardial infarction, or when complications such as embolization, arrhythmias or bronchopneumonia ensue.

The pathogenesis of shock in acute myocardial infarction is not entirely clear, but most probably the symptoms of shock are due to the sharp and sudden reduction of the cardiac output resulting from myocardial injury (p. 214). Shock due to cardiac infarction may sometimes be distinguished from that due to peripheral vascular failure by the frequent presence in the former of dyspnea and orthopnea and distention of the peripheral veins. The degree of shock does not always correspond to the size of the infarct, for the extent of the infarct is not necessarily an accurate measure of the severity of the chemical and physiologic disturbances in the heart muscle. Moreover, some nervous mechanism may be concerned, the behavior of which varies in different persons.

Circulatory Dynamics in Shock due to Myocardial Infarction. There are as yet insufficient studies of the *circulatory dynamics* during the stage of shock in acute myocardial infarction. But it is certain, even allowing for technical deficiencies in its determination, that the *cardiac output* is sharply diminished. Grishman and Master,[68] using the Wezler-Boeger method (p. 135), found the cardiac output distinctly diminished in 5 cases with acute coronary occlusion. Usually the cardiac output fell rapidly, reaching its lowest point on the second or third day, after which it rose gradually and maintained a constant level after the tenth day. By means of the ballistocardiograph, Starr and Wood[151] determined the cardiac output to be normal or diminished in the first week after cardiac infarction. If normal during this acute phase, it tended to diminish subsequently, reaching the lowest limit between the third and fifth week, and recovering thereafter. The left ventricular work, as calculated from the cardiac work and blood pressure, followed a similar course. However, the blood pressure did not always keep pace with the drop in cardiac output, for the latter was often ebbing after the blood pressure had begun to rise.

The *venous pressure* is frequently normal or low and the peripheral veins are collapsed.[57] In some cases of shock following acute myocardial infarction,

notably those with a history of previous infarction or heart failure, the venous pressure may be elevated and the veins distended. Occasionally there is engorgement of the cervical veins with elevation of venous pressure, while the antecubital veins are collapsed and their pressure diminished. Fishberg[56] believes that this discordance is due to a compensatory vasoconstriction of the arterioles of the extremities, which tends to maintain the arterial blood pressure and divert blood in favor of the brain and heart. Therefore, the venous return from the head is relatively normal and the cervical veins are not collapsed as are the peripheral veins. Finally, in many patients without a previous history of congestive failure in whom there is a combination of shock with left ventricular failure the systemic venous pressure is normal, but there are evidences of pulmonary congestion.[152]

A diminution in the *circulating blood volume* was noted by Fishberg et al.[57] in a number of patients with shock due to acute myocardial infarction; the blood volume tended to rise as the patient recovered from shock. That this was not the primary cause of the shock was indicated by the detection of a normal circulating blood volume in other patients with shock. Stead and Ebert[152] found evidence of slight *hemoconcentration* which they thought might be due to a loss of fluid into the lungs.

The *circulation time* is often prolonged because of shock itself or because of the frequent association of pulmonary congestion.[144]

3. Cases Dominated by Acute Left Ventricular Failure. A sudden attack of pulmonary edema is often the first and may be the dominant manifestation of acute myocardial infarction. The attack may appear suddenly and without warning, causing thoracic oppression and intense, suffocating dyspnea and orthopnea. Sometimes, however, it follows hours or days after premonitory substernal pain or recovery from the earlier stage of shock.

The respirations become noisy and asthmatic or bubbling in character. A copious white or pinkish foam may be coughed up or merely wells up from the bronchopulmonary passage and out of the oral cavity and nasal passages. Retrosternal pain may be absent or slight, or if moderately intense it is usually overshadowed by the profound dyspnea and sense of suffocation. Patients in this group may be deeply cyanotic or may present a pale or ashen cyanosis due to the combination of pulmonary edema with shock. Particularly in elderly persons and in the presence of both shock and left ventricular failure or after opiates, there may be *Cheyne-Stokes respiration.*

Lesser grades of pulmonary congestion due to acute left ventricular failure are also common. The onset may be characterized by episodes of paroxysmal nocturnal dyspnea. The wheezing respiration and cough associated with diffuse bronchial rhonchi and distention of the chest may provoke a diagnosis of bronchial asthma. More commonly such episodes of cardiac asthma are associated with the characteristic pain of acute myocardial infarction, or they appear after pain and evidences of shock have subsided. If myocardial infarction begins with massive pulmonary edema, the patient may succumb rapidly or if he recovers he may become subject to less severe left ventricular failure characterized by recurrent cardiac asthma, orthopnea or dyspnea on slight exertion. Cough with or without expectoration and hemoptysis may also be present. Moist râles are usually audible at the base of the lungs and the second pulmonic sound may be accentuated. In these cases the circulation time is prolonged, but the venous pressure may be normal or elevated.

Since myocardial infarction affects the left ventricle almost exclusively, it is not surprising that manifestations of left ventricular failure are common. Sudden inability to expel the venous return results concomitantly in pulmonary congestion and in deficient cardiac output (shock). Some evidence of pulmonary congestion, as denoted by râles at the base of the lungs, is very frequent whether the dominant manifestation is pain or shock or congestive heart failure.

4. Cases Dominated by Manifestations of Right-Sided Heart Failure. While evidences of left-sided heart failure, usually combined with varying degrees of pain and shock, are common even with the first acute myocardial infarction, right-sided heart failure develops rarely during the first attack, and then only after the acute symptoms have subsided. However, with the second or subsequent infarction, evidences of right-sided congestive heart failure appear with increasing frequency and occasionally dominate the clinical picture. The peripheral veins become engorged and the venous pressure elevated.[148] Usually the liver becomes enlarged and it may be tender. Peripheral edema may be present but usually is a late development. Right-sided heart failure after myocardial infarction is always associated with left-sided failure. Dyspnea, orthopnea and attacks of cardiac asthma usually persist, but they are often at least partly alleviated with the development of right-sided failure. Basal râles are usually audible and the circulation time remains prolonged. The symptoms and signs of right-sided heart failure may emerge during the first week after myocardial infarction, but usually they develop after many weeks, as the patient is convalescing and resuming some degree of physical activity. Sometimes rapid enlargement of the liver and peripheral venous engorgement may appear within a few hours after the occurrence of chest pain.

Occasionally the development or intensification of right-sided heart failure is the major or sole feature of an attack of acute myocardial infarction. In most of these cases the patient is one who has had a previous attack of myocardial infarction, following which he has continued to experience angina pectoris or paroxysmal and exertional dyspnea. Then without characteristic symptoms of acute myocardial infarction the signs and symptoms of right-sided heart failure develop more or less rapidly over a period of days or weeks.

Less frequently patients of middle or advanced age without previous cardiac symptoms or evident cardiac disease experience progressive dyspnea and display signs of left and right-sided congestive heart failure. That these clinical manifestations are the result of a fresh myocardial infarct is demonstrated either by definite electrocardiographic changes or by pathologic findings at autopsy. The occurrence of right-sided heart failure after coronary occlusion is dependent on widespread myocardial damage, which implies the existence of multiple or large infarcts, fresh or old.

5. Cases Dominated by Complications. Occasionally none of the above-mentioned striking symptoms are present or they appear in such mild form that they are overlooked. The first conspicuous symptom of acute myocardial infarction may be that of a complication whose relation to the cardiac infarct may or may not be recognized. These complications, which are discussed in detail below (p. 454), include cerebral or other embolization and arrhythmias.

Sometimes cardiac infarction results in prompt and *sudden death* in patients who may or may not have suffered from angina pectoris or other evidences of coronary disease (p. 457).

Associated and Minor Symptoms

I have depicted the clinical features of acute myocardial infarction as distinct integral groups, but I wish to reemphasize that the main symptoms of pain, shock and heart failure are usually associated in the same patient, although one or the other may predominate at different stages of the disease. It should also be reaffirmed that quite frequently these symptoms do not appear in the striking form in which they have been described and that they are often mild in intensity and brief in duration. Indeed it is probable that instances of myocardial infarction with mild symptoms of brief duration are more frequent than is generally recognized, for postmortem studies indicate that there are many more coronary occlusions than are or could be recognized clinically. Many patients do not suffer severely enough to warrant the summons of a physician.

There are many less specific accessory symptoms which accompany but are overshadowed by the major clinical features enumerated. Sometimes when cardiac pain is relatively mild and evanescent and there are no distinctive symptoms of shock or congestive heart failure, these accessory or minor symptoms may dominate the clinical picture.

Gastrointestinal Disturbances and Abdominal Pain. Symptoms classified loosely as *"indigestion"* occur so frequently that cardiac infarction was formerly often mistaken for an attack of acute indigestion. Nausea and vomiting are common, especially when pain is severe. When the pain extends to the upper abdomen and is associated with vomiting, the clinical picture may resemble that of cholelithiasis, acute cholecystitis, peptic ulcer or urolithiasis. When there are also evidences of shock, it may simulate a perforated ulcer or acute pancreatitis. In other cases the pain is so obscured by the nausea and vomiting that the whole episode is attributed to a gastrointestinal disturbance. It is probable that the nausea and vomiting are due to a vagovagal reflex from the region of the infarcted myocardium to the gastrointestinal tract. Often it is uncertain whether vomiting which occurs only after the administration of an opiate is due to the opiate or to the disease itself.

Diarrhea with or without vomiting is occasionally experienced at the onset of acute cardiac infarction, probably also as the result of a vagovagal reflex. More often *constipation* results from the diminished intake of food, the administration of morphine or its derivatives and the stay in bed.

Abdominal distention and a sense of epigastric fullness are common. If the pain is not severe, they may dominate the clinical picture from the outset, but more often they become conspicuous after the pain has subsided. Self-medication with bicarbonate of soda or other alkalis or carminatives in an unsuccessful effort to relieve these digestive symptoms often precedes the patient's summons of a physician. In some instances abdominal distention and constipation are intensified later in the course of the attack by gastrointestinal and hepatic engorgement due to the development of right-sided heart failure.

Jaundice has been noted rarely. In at least one patient whom I observed, the jaundice was due to a coincident obstruction of the common bile duct by a calculus.

Other Symptoms. The occurrence of intense prostration or collapse due to shock has been mentioned, but often only a moderate sense of *weakness* accompanied by cold perspiration and perhaps slight dizziness represents the total or dominant symptomatology of an attack. Weakness is a common and con-

spicuous feature which persists long after most or all of the acute symptoms of cardiac infarction have disappeared. It is especially common in patients who develop distinct signs of congestive heart failure, but it may represent the only or the chief residual symptom.

Palpitation is a common complaint, especially after the more conspicuous symptoms have subsided. It may become particularly annoying when it is associated with extreme tachycardia or other arrhythmia or when there is a sinking or fluttering sensation of irregular, premature or dropped beats.

Urinary symptoms are rarely prominent, but there may be a reduction or more rarely an almost complete suppression of the urinary output (p. 440).

Symptoms referable to the central nervous system are relatively uncommon except for the mental torpor or collapse associated with severe cardiac shock at the onset of the disease. But occasionally they are the most impressive features of the disease, while the coronary occlusion is unsuspected.[42] Mental torpor or confusion, dizziness or vertigo, loss of memory, stupor or coma is likely to occur in elderly patients with cerebral arteriosclerosis, in whom the blood flow to the brain is further diminished by the sudden drop in blood pressure. Hemiplegia and aphasia may result early from cerebral vascular thrombosis with encephalomalacia or hemorrhage, or after the first week from cerebral embolization arising in ventricular mural thrombi. Occasionally there are epileptic convulsions or delirium. Attacks of convulsions and faintness or syncope (Adams-Stokes syndrome) may be due to complete heart block or episodes of ventricular fibrillation with resulting intervals of asystole and cerebral ischemia (p. 302). Cheyne-Stokes respirations may appear, especially in elderly persons with cerebral arteriosclerosis or when intense cerebral ischemia results from extreme cardiac shock (for pathogenesis, see p. 116). The administration of opiates and the advent of left ventricular failure with consequent overventilation and acapnia may be important contributing or precipitating factors. Coma may be due to a complicating diabetic acidosis.

Other symptoms occur rarely. *Hoarseness* due to the paralysis of the left recurrent laryngeal nerve may result from compression of that nerve by the engorged left pulmonary artery in left ventricular failure.[55, 84]

Hiccup has been noted rarely[172] and has been attributed to associated diaphragmatic pericarditis with irritation of the phrenic nerve.

OBJECTIVE MANIFESTATIONS OF ACUTE MYOCARDIAL INFARCTION

General Appearance and Behavior

In the classic case characterized by severe pain, the patient presents a striking contrast to the person suffering from a paroxysm of angina pectoris. Although the pain is similar in quality and location, the patient with angina pectoris usually remains utterly quiet, fearful of every motion or even of every breath, having discovered that rest relieves and activity kindles or intensifies the pain. With the onset of pain from an acute myocardial infarction, he may at first also try to remain motionless. But with persistence and increasing intensity in the pain he becomes extremely restless. Sometimes his futile efforts to relieve the pain lead to bizarre forms of behavior. He may tear or clutch at his chest as if to remove a weight or release a vise-like band, or he may massage it vigorously as one does a cramp in a leg. He may thrash from side

to side in an effort to find a comfortable position in bed, or he may alternately get up and sit down or pace the floor as he moans with pain. I have seen patients on the floor, crouching on their knees, as some do when suffering from a biliary or renal colic. Occasionally a patient with acute cardiac infarction purchases some relief by extending his arms upward as if to enlarge the capacity of the chest. He may be found lying in bed with his hands above his head, clutching the head of the bedstead. On one occasion I found a patient suspended by his hands from the top of a door. As a rule, however, when the physician arrives the patient is found in bed where he is squirming restlessly, holding his chest and complaining of pain.

When shock is the predominant feature, the patient's appearance is characterized by listlessness or prostration as he lies quietly in bed. Although he may acknowledge the presence of pain, he does not complain of it spontaneously. His vocal responses, in general, are low and brief as if every word is an exhausting effort. Occasionally he is somewhat confused and disoriented or he may appear dazed. His countenance is of ashen pallor and his lips and fingertips faintly cyanotic. His hands and feet and the tip of his nose are cold and moist. There may be a bluish-red mottling of the skin (cutis marmorata). On one occasion I have seen striking acrocyanosis of the fingers and toes undoubtedly due to exaggerated arteriolar constriction. From the beginning, or as the shock clears after the first few days, the patient's appearance is gradually modified by the intrusion into the picture of a variable degree of left-sided heart failure.

A somewhat different appearance is presented by the patient whose attack of myocardial infarction is evinced predominantly by acute pulmonary edema. He is found propped up high on several pillows, gasping for breath, his neck veins often engorged and his lips and skin distinctly cyanotic. Between gasps he may complain of a massive oppression over the chest. This may be described as a pain but more often as a sense of suffocation. He may express a fear of impending death. He may cough occasionally; the sputum produced may be blood-tinged. In extreme cases there is a copious foamy pink-stained fluid exuding from his mouth and sometimes even from his nostrils. Frequently, moderate or severe shock is associated; then the cyanosis has an ashen hue, the extremities are cold, and the peripheral veins in the extremities may be collapsed although those in the neck are tense. The appearance described above may be observed only if the patient is seen soon after the inception of his symptoms. Pulmonary edema often clears with remarkable speed, either spontaneously or after an opiate; the morning after the attack the patient may appear quite comfortable or only moderately dyspneic and orthopneic. In the more ominous cases, however, pulmonary edema may persist for several days until the fatal end, or disappear and recur several times until the patient succumbs.

These, the most dramatic and most severe clinical pictures, usually represent only the onset or first few days of the attack. Some patients, appearing perfectly well, walk into the physician's office to report a pain that has already disappeared, or dyspnea which disturbs them only at night or recently developed symptoms of indigestion. Many others are sufficiently alarmed to go to bed and call a physician, but present no striking abnormalities in appearance or behavior as they complain of persistent chest pain and perhaps also weakness, perspiration, nausea or abdominal distention or breathlessness.

The Heart

Physical examination of the heart often reveals surprisingly little in view of the extent and severity of the cardiac damage. Slight or moderate enlargement of the heart, such as might be attributed to previous or present hypertension, is usually difficult to discover by percussion. This difficulty is often enhanced by hyperresonance due to associated pulmonary emphysema. Estimation of the cardiac size from the position of the apical impulse may also be foiled because the latter is impalpable or vague and diffuse. When percussion of the cardiac borders and palpation of the apical impulse are satisfactory, there is often no evidence of cardiac enlargement. However, in the presence of congestive heart failure the heart may be so enlarged that this is readily determined by percussion and palpation.

Auscultation of the heart may be more revealing, although frequently this also discloses no significant abnormality. In many cases the heart sounds are faint in volume and muffled in quality. The first sound in particular is usually faint and low pitched. It may be indistinguishable from the second sound, with a consequent tic-tac rhythm. A soft blowing murmur at the apex, probably due to a functional mitral insufficiency, is most often heard in instances of second or multiple infarction in which there is some degree of left ventricular dilatation. An aortic systolic murmur may also be noted; its pathogenesis is uncertain but it is usually attributed to arteriosclerotic changes in the ascending aorta near the aortic ring. When hypertension persists despite the myocardial infarction, the second aortic sound may be accentuated or even reduplicated. Often in cases characterized by left ventricular failure with pulmonary hypertension the second pulmonic sound is accentuated and may be louder than the second aortic sound, even when there is systemic hypertension.

Gallop rhythm and pericardial rub have a more specific diagnostic value. I have heard a gallop rhythm in more than one third of the patients whom I have been able to observe within the first few days after the onset of the attack. Shillito et al.[148] noted it in 8 of their 50 cases. The gallop rhythm is usually best heard at or slightly medial to the apex of the heart, but it may be most clearly audible in the fourth interspace near the left sternal border. Occasionally the gallop can be detected over a wide area of the precordium. It is protodiastolic or presystolic in time, more frequently the latter if the ventricular rate is rapid.

In their study of the heart sounds in 80 cases of cardiac infarction, Master and Friedman[104] noted an auricular sound in 83 per cent, which was sufficiently accented in 33 per cent to produce an audible presystolic gallop. In 47 per cent there was a third heart sound early in diastole; in 8 per cent this sound was accented and audible as a protodiastolic gallop. In 6 per cent there was a superimposition of the auricular and third heart sound causing an audible summation gallop. Thus there was an audible gallop in almost one half of their cases.

Since gallop rhythm is probably associated with left ventricular dilatation (p. 126), it is usually encountered in cases in which heart failure is significant. Gallop rhythm most frequently appears in the first day or two after the infarction and disappears as cardiac function is adjusted. But if conspicuous heart failure continues, gallop rhythm may also persist. Sometimes in cases with

severe shock at the onset of the attack there is no audible gallop during the first few days. But as shock subsides and left ventricular failure becomes more prominent, gallop rhythm may become manifest.

A *pericardial rub* has been noted in about one fifth of the cases in several reported series.[22, 14] Undoubtedly it would be heard more often if it were deliberately sought and if patients were examined frequently soon after the onset of the attack. For the rub appears intermittently, persisting briefly at each appearance. It may first be audible a few hours after the attack, but most commonly on the second or third day; thereafter it recurs usually only for a few days. Occasionally with large infarcts or progressive myocardial infarction, a pericardial rub persists continuously for many days.

The pericardial rub is usually heard best just inside the apical impulse or along the left border of the sternum, but it may be audible over a large part of the precordium or localized over the lower portion of the sternum. A pericardial rub is not indicative of anterior infarction as is commonly believed; it may be heard also following posterior ventricular infarction.[158] It is much more likely to appear when there is a generalized acute fibrinous pericarditis than with a localized pericarditis, and generalized pericardial inflammation may follow posterior as well as anterior wall infarction. In 3 out of 5 cases of generalized pericarditis associated with an audible rub, Stewart and Turner found the infarcted area limited to the posterior wall.

A pericardial effusion following myocardial infarction has been reported rarely.[149, 140] It is probably overlooked in most cases in which it occurs. Nichol[116] reported a pericardial effusion sufficiently large to necessitate a paracentesis. A pericardial rub may be audible even when the effusion develops. A distinction should be made between pericarditis with effusion and a noninflammatory hydropericardium representing a serous transudate due to advanced congestive heart failure. The pericardial effusion may consist of pure blood (hemopericardium), a consequence of cardiac rupture.

The Pulse

There is usually an acceleration in the pulse rate to between 100 and 110 per minute, especially during the febrile stage. At the very onset the pulse rate may be rapid in the presence of shock or heart failure, even when the temperature is normal. In the absence of noticeable heart failure, shock or fever, the pulse rate is usually normal. Occasionally there is a sinus bradycardia with a pulse rate of 60 per minute, and rarely complete heart block with a pulse rate below 40. The rhythm of the pulse is usually regular, but premature beats occur commonly and occasionally other arrhythmias may produce irregularity or a striking quickening of the pulse (p. 452).

The Blood Pressure

As a rule, cardiac infarction is followed by a fall in the blood pressure. But initially there may be a transient rise even when there are other clinical evidences of shock.[171] The blood pressure usually falls further in patients with hypertension than in those with a normal pressure prior to the attack. The eventual pressure may decline to 90 mm. Hg or lower, regardless of the blood pressure before cardiac infarction. But patients with previous hypertension usually have higher pressure after infarction than those with previously normal

pressure. The diastolic as well as the systolic pressure is reduced, but not to the same degree. In consequence the pulse pressure is usually significantly diminished. In contrast with these usual findings, Yater et al.[180] reported that the blood pressure remained normal or returned to normal in 70 per cent of soldiers between the ages of eighteen and thirty-nine who had survived an attack of acute coronary thrombosis.

The fall in blood pressure usually occurs rapidly, sometimes after several hours, but more often on the second day of the attack. Occasionally there is a gradual progressive decline and rarely it is delayed for a week.[29] In early fatal cases, often associated with blood pressures below 90 or 80 mm. Hg, there may be little or no rise in pressure up to the end. But in most cases a low point is reached some time in the first week or more often in the second or third week.[106] After one to three weeks at this level, there is a gradual progressive rise. However the blood pressure seldom returns quite to its initial level until after convalescence. About two thirds of the patients with previous hypertension eventually regain their hypertension. In some of these, hypertension reappears within several weeks or months after moderate activity is resumed, but in others one to three years may elapse before the previous levels of high blood pressure are attained.[120] Occasionally I have observed the blood pressure dive precipitously on the first day after an acute coronary occlusion and rise sharply on the following day, almost but not quite to its initial level. In fatal cases, the blood pressure may remain at its lowest hypotensive level until the patient succumbs.

The fall in blood pressure after acute myocardial infarction is probably related chiefly to the reduction in cardiac output, although these two do not follow a uniformly parallel course. Compensatory vasoconstriction is an important modifying factor. This and the later recovery in cardiac output account in most cases for the subsequent rise in blood pressure and restoration to the original level. But in about one third of the patients with previous hypertension the blood pressure, after cardiac infarction, remains within a normal range for at least many months, even though there is no longer any evidence of a diminished cardiac output, and cardiac function appears well compensated. In these patients it must be assumed that the persistent diminution in blood pressure is due to a permanent relaxation in the peripheral arterial resistance.

Fever

Usually within twenty-four to forty-eight hours, and occasionally as early as four to eight hours after the onset of acute cardiac infarction, there is a moderate rise in temperature to 100° to 102° F. But fever up to 104° or 105° has been observed not infrequently. Shillito et al.[148] noted fever at some time in all of their 50 cases of uncomplicated myocardial infarctions. The temperatures must be taken rectally and at regular intervals to discover slightly abnormal elevations.

The temperature usually reaches its peak on the third or fourth day and persists altogether for two to four days, but occasionally longer. As a rule, the temperature returns to normal by the seventh or eighth day. However, progressive myocardial infarction or the development of complications may prolong the duration of the fever, or may cause a recrudescence if the temperature has already returned to normal.

Leukocytosis

An increase in the white blood cell count occurs almost invariably and early, occasionally within two hours after the onset of the attack.[92, 169] Most frequently the leukocytosis is detected on the second or third day. As a rule the white blood count varies between 12,000 and 15,000, but counts between 15,000 and 20,000 are not rare. There is an associated polynucleosis of 75 to 90 per cent and there may be a slight shift to the left, that is, the percentage of young (nonsegmented) forms is increased.

The leukocytosis recedes after a few days and usually disappears by the end of a week. Persistence of the leukocytosis thereafter or the presence of extremely high white blood counts suggests the development of a complication such as pulmonary or other embolism, bronchial pneumonia, or progressive myocardial infarction.[97] However, Levy[90] has observed a white blood count of 33,000 in an uncomplicated case of acute myocardial infarction.

The presence of a leukocytosis may be a valuable diagnostic aid in dubious cases of myocardial infarction. The white blood count is often a more sensitive index of cardiac infarction than the temperature, because there may be a definite leukocytosis when the presence of fever is uncertain as in cases with a temperature around 100° F.[92] Furthermore, the leukocytosis usually develops before fever.

Increased Sedimentation Rate

The rate of sedimentation of the erythrocytes is almost always increased following an acute myocardial infarction.[132] Rabinowitz et al.[129] noted this in all of the 29 cases which they reported and Shillito et al.[148] in 49 of 50 uncomplicated cases of cardiac infarction. The increased sedimentation rate is attributed to a change in the composition of the plasma due to the absorption of products of the necrotic heart muscle.[71, 117]

Usually the increased sedimentation rate is first noted on the second or third day of the attack and persists for several weeks until the infarct is healed. The accelerated rate may begin within a few hours after the acute myocardial infarction, attain its most rapid phase in four or five days and persist for two to six months.[85] Therefore, repeated determinations are usually made as a guide to the progress of healing and management of the patient's activities. In this respect observation of the sedimentation rate is more valuable than that of the temperature and white blood count, for an increased sedimentation rate persists after fever and leukocytosis have disappeared. Furthermore, the sedimentation rate is sometimes a more sensitive index of myocardial infarction than the temperature and white blood count, for it may be increased after premonitory pain before there are other objective evidences of myocardial infarction. This may aid in distinguishing whether such pain represents a paroxysm of angina pectoris or whether it presages the advent of myocardial infarction. Riseman and Brown[132] found the sedimentation rate slightly increased in 50 per cent of their cases of angina pectoris, but this suggests that some myocardial necrosis may have been present. In the classic cases of acute myocardial infarction there does not appear to be a good correlation between the degree of increase in sedimentation rate and the severity of the attack or the prognosis.

Delaney and Keyes[39] observed a *shortening of the Weltmann serocoagulation band* in cases of myocardial infarction, beginning on the second or third day and reaching its minimum by the fifth or the seventh day. Healing of the infarct was associated with progressive extension of the coagulation band. They suggested that this laboratory test was a more valuable diagnostic and prognostic laboratory aid than the sedimentation rate because it is less altered by other coexistent factors. I have had no personal experience with this test.

Other Laboratory Findings

The examination of the *urine* usually discloses no significant abnormality. In patients with hypertension, a faint trace of albumin and occasional hyaline casts are often found. These findings are also associated with the development of right-sided heart failure.

Glycosuria and hyperglycemia have been observed not infrequently in patients with and without a previous history of diabetes.[89, 128, 48] In diabetics, who are especially subject to acute myocardial infarction, glycosuria may reappear during the attack if previously controlled by diet or insulin. Occasionally an acute myocardial infarction may precipitate diabetic acidosis and coma, with obscuration of its clinical picture. Patients with these complications often succumb despite prompt and adequate treatment of the metabolic disturbance.

The occurrence of hyperglycemia and glycosuria in patients without a previous history of diabetes has been explained as due to adrenal stimulation in shock, to circulatory disturbances in the vegetative centers of the brain, or to the development of a manifest diabetes in a latent diabetic as a result of the acute cardiac infarction. Recently Goldberger et al.[63] supported the latter theory and refuted the assumption that the hyperglycemia and glycosuria were insignificant and transient. These observers performed glucose tolerance tests repeatedly over a period up to thirteen months on 14 patients with acute myocardial infarction, none of whom had a history of diabetes. They concluded that 6 presented definite evidence of diabetes, 4 yielded abnormal glucose tolerance curves, and 4 normal curves. In several instances hyperglycemia and abnormal glucose tolerance curves were absent soon after the attack and appeared months later. The tendency for the curves to become more and more abnormal over a period of months led these investigators to conclude that the hyperglycemia was not transient and that it indicated latent diabetes in these patients.

Oliguria, sometimes of extreme degree, has been noted in association with intense shock, and there may be anuria for as long as twenty-four hours.[72, 131] These disturbances may result not only from cardiac shock and a consequent reduction in blood flow through the kidneys, but also in part or entirely from prerenal deviation of fluid caused by drenching perspiration, vomiting, minimal fluid intake or the development of right-sided heart failure. Sometimes urinary suppression results from an associated prostatic obstruction, the symptoms of which are intensified by bed rest. While oliguria is usually accompanied by a concentrated urine of high specific gravity when the kidneys are normal, occasionally in severe shock the urine may be pale and its specific gravity fixed at a low point indicative of renal impairment. This is due to a sharp diminution in the renal blood flow; restoration of normal renal function almost always follows recovery from the acute infarction.

Hematuria may appear as a consequence of renal infarction, secondary to

emboli arising from left ventricular mural thrombi. Unilateral hemoglobinuria has been reported.[96]

Creatinuria may result from increased catabolism following myocardial infarction.[2]

Chemical examination of the blood may disclose a hyperglycemia, which has been discussed above. Although this may denote latent diabetes, it should not in itself be interpreted as an indication for the administration of insulin (p. 494).

Azotemia appears occasionally and rarely the blood urea nitrogen may exceed 60 mg. per 100 cc.[154] It is usually associated with severe shock and other factors which cause oliguria. Blood lactate, pyruvate and amino acids are slightly elevated.[2]

Roentgenologic Findings in Acute Cardiac Infarction

The roentgenographic examination of the heart often discloses no abnormality following acute cardiac infarction or only slight alterations due to previous hypertension.

Disturbances in the pulsations of the left ventricle can often be ascertained by fluoroscopic examination[105] and by kymography.[70, 162, 61] These disturbances result from the diminution or absence of contraction of the infarcted heart muscle or from its passive expansion during systole. The following fluoroscopic abnormalities may be noted:

1. Localized, more or less extensive *absence of pulsation* along the left lower border of the heart (left ventricular contour).

2. Local *reversal of pulsation* of the left ventricle, i. e., there may be a systolic expansion of one part of the left ventricular contour while the remainder contracts. For orientation the observer may view the aortic pulsations. Distention of the aorta marks the onset of ventricular systole. In addition to the above abnormalities, kymography may also disclose diastolic splintering, denoted as marked irregularities during diastole.[162]

Several sources of error should be considered: (1) In large hearts the apical region, a frequent site of infarction, may disclose no pulsation or even reversal of pulsation when there is no infarction. A pericardial tumor may produce reversal of pulsation.[143] (2) Accurate fluoroscopic observation of the pulsations of the heart is often difficult, especially when there is a large extrapericardial triangular shadow (due to a fat pad). (3) The apical and adjacent supra-apical region normally contracts slightly later than the more basal portion of the left ventricular contour. This may be misinterpreted as a reversal of pulsation. Roentgenologic diagnosis is further hampered by the fact that most patients with acute myocardial infarction are too ill to be subjected to such examination. The findings of absence, diminution or reversal of ventricular pulsation in cases of myocardial infarction may be observed with old as well as recent infarcts, and with posterior as well as anterior infarction.

Other roentgenologic abnormalities may result from complications of myocardial infarction, such as pulmonary congestion due to heart failure,[100] pulmonary infarction, pneumonia and ventricular aneurysm. Enlargement of the heart in coronary occlusion has been discussed above (p. 420).

Calcification of a myocardial infarct, rarely with bone formation, may be observed roentgenologically.[26, 19] However, cardiac infarction is not the only

cause of myocardial calcification. Calcification of the coronary arteries, of mural thrombi in mitral stenosis or after cardiac infarction, of the pericardium, of cardiac aneurysms and of the mitral or aortic valves must be differentiated.[17]

Electrocardiographic Changes in Acute Cardiac Infarction

Acute cardiac infarction usually produces alterations of the electrocardiogram which, when studied early and by serial examination at brief intervals, are diagnostic of the disease. The electrocardiographic changes following cardiac infarction are determined not by the causative coronary occlusion as such but by the location, extent and irreversibility of the consequent myocardial anoxia and necrosis. When coronary occlusion occurs without infarction there may be no significant electrocardiographic abnormality despite the occlusion, or only transient RST depressions or inversion of T waves associated with temporary and reversible myocardial anoxia.

The process of cardiac infarction is an active and changing one, during which the absolute and relative extent of necrosis and anoxia varies until healing occurs. The progressive changes are documented by corresponding electrocardiographic alterations which differ according to the interval since infarction and the degree of healing. This evolutionary nature of the electrocardiographic patterns is an important diagnostic feature. After the infarct has healed, the electrocardiogram may continue to disclose abnormalities suggestive of the occurrence and even of the localization of previous infarction, but these changes are rarely as conclusive or striking as those accompanying acute cardiac infarction.

Factors Limiting Electrocardiographic Diagnosis. In most cases of acute cardiac infarction, the electrocardiogram discloses changes which not only are distinctive for this disease, but also reveal accurately the location of the area of infarction.[9, 54, 80] However, in a variable percentage of cases the electrocardiographic changes may not be typical of acute myocardial infarction or do not disclose its location under the following circumstances:[9]

1. Multiple infarcts occur commonly. The electrocardiographic changes produced by the fresh infarct may be neutralized by those of previous infarcts. Or the multiple infarcts may produce diffuse myocardial damage, the electrocardiographic representation of which is indistinguishable from that of other varieties of diffuse myocardial disease.

2. The presence of a bundle branch block may obscure the electrocardiographic pattern of acute cardiac infarction (p. 450).

3. When extensive pericarditis complicates acute myocardial infarction, the electrocardiographic changes may be dominated by and diagnostic of acute pericarditis (p. 468).

4. The number of electrocardiograms taken may be insufficient, or the time at which these are taken in relation to the occurrence of the infarct may be improper to disclose characteristic changes.

5. Previous treatment by digitalis produces RST and T wave changes which may conceal those of myocardial infarction.

6. The position of the heart in the thorax, i. e., a decidedly transverse or vertical heart, by its effect on the electrocardiogram may obscure the localization of the infarct.

7. Electrocardiograms taken shortly before the death of the patient may fail to disclose the typical electrocardiographic changes of myocardial infarction.

Typical Electrocardiographic Patterns in Standard Leads. The earliest changes affect the RST segments[121] and are usually observed within twenty-four hours, rarely within a few hours after the attack.[32] In some instances the ST changes appear only after two or three days or even after a week or longer.[159] However, according to the experimental observations of Bayley and associates,[13] a primary inversion of the T wave may precede RST segment deviation.

The first significant abnormality is an elevation of the ST segment above the isoelectric level in lead I or lead III or in precordial leads. Characteristically this segment presents a "high take-off" from the descending limb of the R wave and its slope is convex upward.[122] This elevation is transient, lasting usually a few hours or days, but it may persist for two to three weeks. The upward convexity of the RST segment often remains after it reaches the isoelectric level.

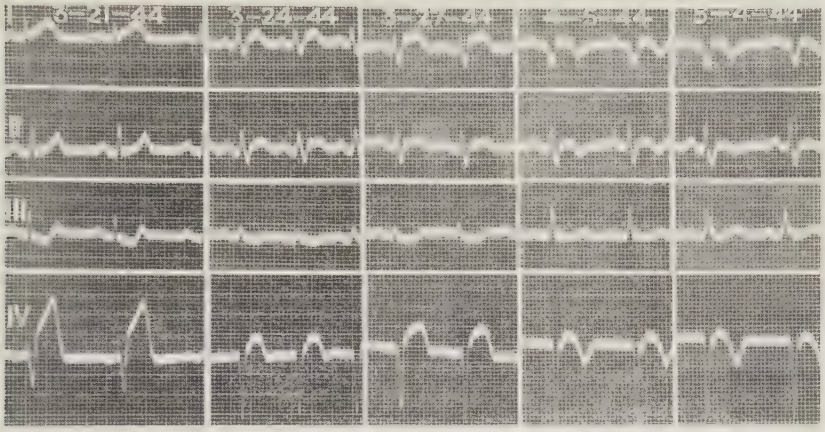


Fig. 49. Acute coronary occlusion. Anterior wall infarction. Progressive changes. R-T elevations in leads I and IVF with depression in lead III. Subsequent T wave inversion. Absence of initial deflection (presence of Q waves) in IVF and lead I.

Subsequent changes[137, 124, 32] produce a progressive regression of the ST segment to the isoelectric level and a concomitant lowering and eventual inversion of the T wave in the same lead (Fig. 49). Simultaneously there is often a conspicuous and sometimes broad Q wave in the same lead.[174]

Parkinson and Bedford,[124] and Barnes and Whitten,[10] observed that the changes in the ST segments and T waves fell into two common patterns which they designated as the T_1 and T_3 types. Subsequent studies of the initial ventricular complex[123, 174, 8] enlarged these patterns into the Q_1-T_1 and the Q_3-T_3 types. A correlation of electrocardiographic and necropsy findings demonstrated that the Q_1-T_1 pattern was associated with an acute or healing infarction of the anterior wall and the Q_3-T_3 pattern with an acute or healing infarction of the posterior wall of the left ventricle.

Theoretical Basis of Electrocardiographic Changes in Acute Myocardial Infarction.[11, 12, 79] Living, resting heart muscle is believed to be electrically active or polarized, with doublets of negative and positive charges arranged along the cell membranes. The negative charge (sink) is on the inside, and the positive charge (source) on the outside of the membrane. The activating stimulus in the heart sets off the process of depolarization which proceeds

rapidly from sinus and a-v nodes along the septum and subendocardium of the chamber walls and then more slowly, perpendicularly through ventricular muscle from the subendocardium to the epicardium. Activated muscle is negatively charged with respect to resting muscle, i. e., the positive charge precedes and the negative charge follows the wave of depolarization. Unipolar leads over the left ventricle show a positive initial complex (R or QRS) corresponding to the relative positive potential of the epicardial layer underlying the exploring electrode. When depolarization is complete, there is a period without flow of current (isoelectric interval) denoted by the RST segment. Thereafter there is a slower repolarization documented by the T wave followed by electrical diastole.

RST Deviations. When myocardial infarction ensues after an acute coronary occlusion, a central core of muscle undergoes necrosis and therefore produces no electrical phenomena. This dead tissue is surrounded by a concentric shell of injured tissue which is still alive and therefore partially polarized.[11] The injured tissue in turn is surrounded by ischemic tissue which may be normally polarized in diastole but which experiences a delay in repolarization during systole. During the acute stage of infarction the injured tissue, which is negative relative to ischemic or normal tissue, gives rise to a persistent current of injury. During electrical diastole this current of injury deviates the string from the isoelectric line. But in standardizing the electrocardiogram we start by bringing the string back to the center of the film by means of a compensating current from the control battery. This neutralizes the current of injury during diastole. During the depolarized state, (S-T interval of systole), this neutralizing current is unbalanced and produces a deviation of the RST segment.

When the injured muscle is in the subpericardial region, the current of injury is toward the endocardium and tends to cause an RST depression in a precordial lead. But the neutralizing current responsible for the RST deviation flows in the opposite direction, i. e., toward the surface of the heart. Therefore in the case of anterior wall infarction with subpericardial injured tissue, a precordial lead, facing the advancing wave or positive potential, discloses an elevation of the RST segment. A posterior wall infarct might produce no RST deviation in a precordial lead or a slight depression. In cases of pericarditis in which subepicardial myocardial injury affects both walls universally, RST elevations are also observed in precordial leads. In cases of subendocardial injury, e. g., in certain cases of severe coronary insufficiency without occlusion, the current of injury is directed from subendocardium to epicardium and the neutralizing current is in the reverse direction. Therefore precordial leads over the affected area yield depression of the RST segment.

T Wave Changes. The ischemic area, in contrast with the injured area, is believed to modify only the process of repolarization and is responsible for T wave changes including inversion.[11] When the ischemic area is very large and the injured area absent or small, T wave changes may occur without ST deviations. According to Dressler and Roesler,[46] high T waves precede inversion of the T waves or RST deviations. The high T waves are believed to be part of the injury pattern, possibly due to the release of potassium from the cells.

Q Waves. The dead infarcted tissue gives rise to no current. If it extends transmurally, it may be considered as a window cut out of the ventricular wall.[173] Therefore the negative potential within the endocardial cavity is trans-

mitted through this dead tissue, to a superjacent precordial lead. Instead of the normal positive initial deflection, the initial ventricular complex is downward, i. e., there is either a deep Q wave or QS in a lead placed directly over the infarct.

With healing of infarction, Q waves often persist in the precordial leads because a core of dead, electrically inert tissue remains. On the other hand the injured tissue either dies, becomes ischemic or recovers and the RST deviation therefore disappears. Actually the RST deviations recede when the injured area no longer extends to the epicardial surface. The persistence of T wave changes depends on the presence of ischemic tissue of significant size; this causes aberrations in the repolarization process.

The changes seen in the standard or unipolar limb leads depend on the location of the infarcted, injured or ischemic tissue, the position of the heart and the relation of the latter to the sites of attachment of the extremities to the trunk. If the injured and infarcted zone reaches the epicardium of the anterior wall, there is a Q wave and an elevation of RST in leads I and V_L which face the injured area and a depression of RST in leads III and V_F and V_R facing the relatively normal tissue. In posterior wall subepicardial infarcts, Q waves and elevation of the RST segment appear in leads III and V_F and in esophageal leads at the level of the ventricle E_V. In pericarditis with universal subepicardial involvement of both walls, RST elevations occur in all standard leads since they all face the injured area. But Q waves are absent since there is no transmural dead tissue. In subendocardial injuries, all standard leads usually face normal tissue which is interposed between them and the injured tissue; therefore ST depressions may be seen in all these leads and there are no Q waves due to dead tissue.

Anterior Wall Infarction (Q_1-T_1 Pattern). The Q_1-T_1 type of electrocardiogram is characterized as follows (Fig. 49):

1. At first there is an *elevation of the ST segment in lead I,* and sometimes also in lead II, with a simultaneous depression of ST in lead III (discordant ST deviations). Occasionally ST depressions only or high T waves may precede these discordant changes. According to Dressler and Roesler,[46] high T waves are the earliest and sometimes the leading diagnostic sign of myocardial infarction.

2. The ST_1 elevation appears characteristically convex upward or dome-shaped, with a downward slope toward the T wave.

3. *The T wave in lead I subsequently becomes depressed or diphasic and eventually sharply inverted and* **V***-shaped.* The limbs of the T wave may be symmetrical and the shoulders rounded upward. At the same time the T wave in lead III becomes upright and sometimes exaggerated and sharply peaked[25] (discordant T waves in leads I and III). The T wave deflection in lead II is usually similar to that in lead III, but occasionally is inverted as in lead I.

4. An early frequent change is the appearance of a *prominent Q wave in lead I.* The Q wave may be broad. It is followed usually by a low R wave with or without a subsequent S deflection. This may produce an **M** or **W** shaped QRS in lead I. There may also be a definite *Q wave in lead II.* S_2 and S_3 are often conspicuous. There may be a tendency to right deviation of the electrical axis.

5. After two to four weeks, but often in a few days, the ST elevation in lead I is very slight or disappears, but it may retain its upward convexity, which

slopes sharply downward toward an inverted T wave (coronary T wave,[122] cove plane T wave[137]). The T wave may become upright in a few weeks, but more often after three to six months or longer, or may remain inverted.

Precordial leads[175, 177, 173] may reveal characteristic changes when there is no abnormality in the standard leads or when the latter disclose only suspicious changes (Figs. 50–51).

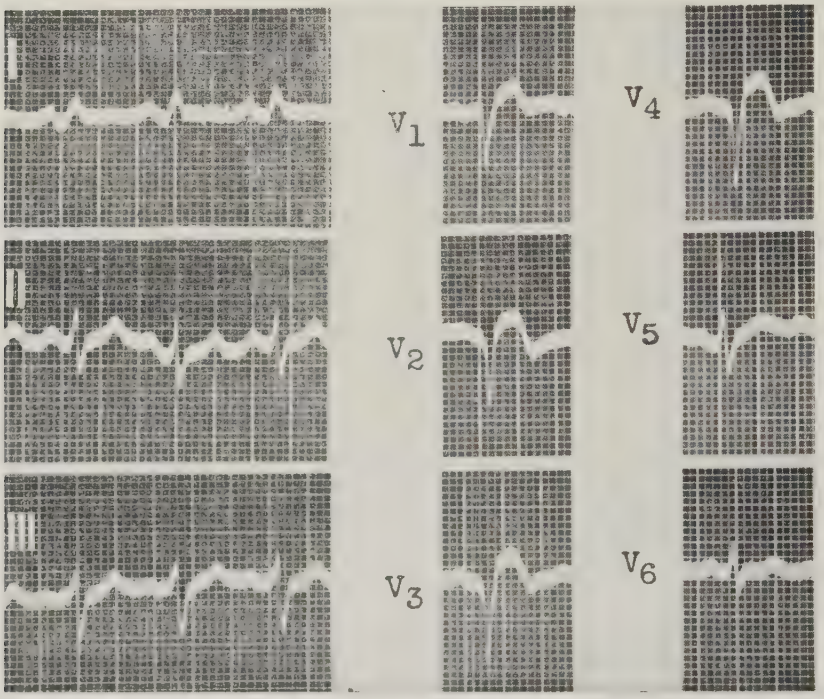


Fig. 50. Acute anteroseptal infarction. Characteristic changes of acute infarction absent or indefinite in standard limb leads. Q waves, RT segment elevations and diphasic T waves in V1-4 overlying anteroseptal wall with relatively normal QRST complexes in V_5 and V_6 overlying apex or anterolateral wall.

1. There is an *early elevation of the ST segment* (more than 2 mm.). Often the ST segment has a characteristic upward convex shape. The ST elevation usually disappears in a few days, but occasionally persists much longer.

2. From the onset, or as the ST segment declines, there appears a *large initial negative deflection (Q wave)* (more than 2 mm.) instead of the normal initial upward deflection. This may be the sole deflection (QS) of the QRS group; if so, it is frequently slurred or notched in its descending limb. Or else the deep Q may be followed by a much smaller R wave and occasionally also by a very small S wave. In the latter instance the QRS may appear **M** or **W** shaped.

3. As the elevated RST segment declines, *the T wave becomes diphasic and then inverted.* The inverted T wave is often large and sharply peaked. Unlike the RST elevations which are quite transient, the T wave inversion usually persists for months and occasionally for years before reverting to normal.

Depending on the extent and location of the infarct, these changes will be

observed in one, two or more of the precordial leads. The presence of an abnormal Q wave may be due to either a recent or an old infarct. A negative T wave in precordial leads is usually abnormal, except in V_1 or V_2 and in children, but it does not denote myocardial infarction unless serial electrocardiograms previously disclosed elevation of the RST segment and progressive T wave inversion. The combination of an abnormal Q and a negative T is strongly suggestive of a previous or recent anterior wall infarct. But in the presence of a normal R wave, a negative T wave may be due to left ventricular strain or axis deviation.

SUBENDOCARDIAL INFARCTION. In some cases of typical clinical myocardial infarction, subsequent pathologic examination discloses extensive necrosis confined to the subendocardial region and due to left or right coronary occlusion

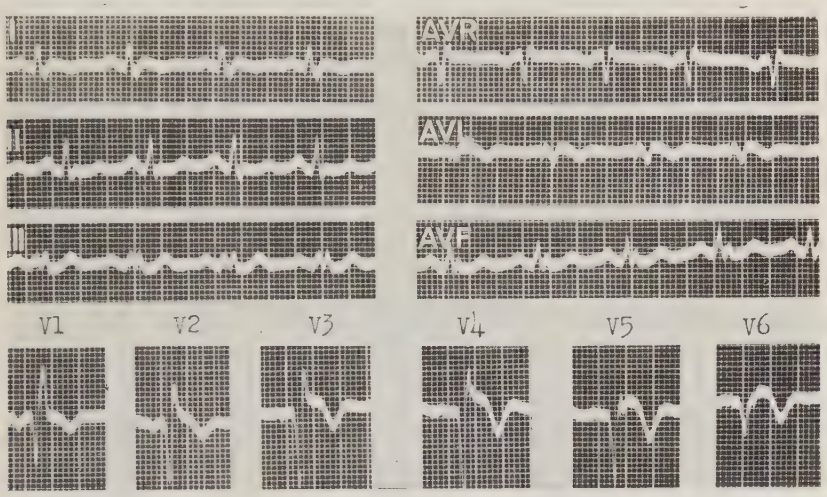


Fig. 51. Anterior wall infarction with right bundle branch block. Wide QRS complex with broad S_1 in standard leads indicative of right bundle branch block. Anterior wall infarction disclosed by Q waves and RT elevations in precordial (V) leads.

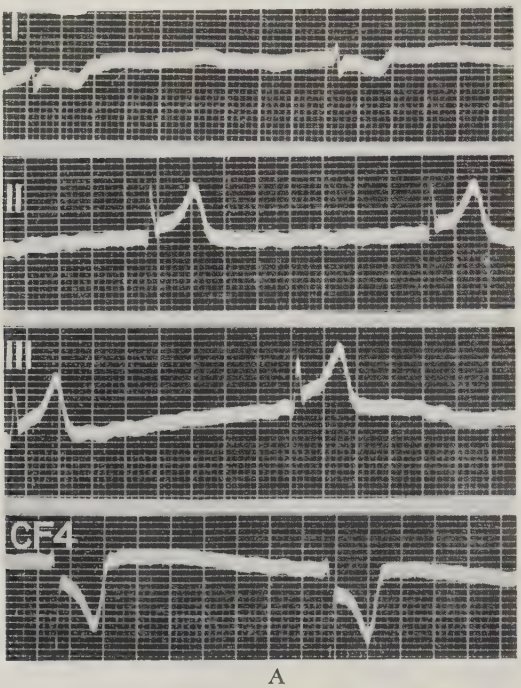
or severe stenosis. In such cases there may be no Q waves or ST segment elevations. For ST segment elevations depend on subepicardial infarction and Q waves on through and through (transmural) infarction. Instead there are striking ST depressions in all the standard leads and the precordial leads. Thus electrocardiographic ST depression alone may signify serious or fatal cardiac infarction and should not be interpreted necessarily as denoting only reversible "coronary insufficiency" or "coronary failure."

ANTEROSEPTAL INFARCTION. An infarct localized in the anteroseptal region may be indicated by the following changes in unipolar precordial leads[113] (Fig. 50):

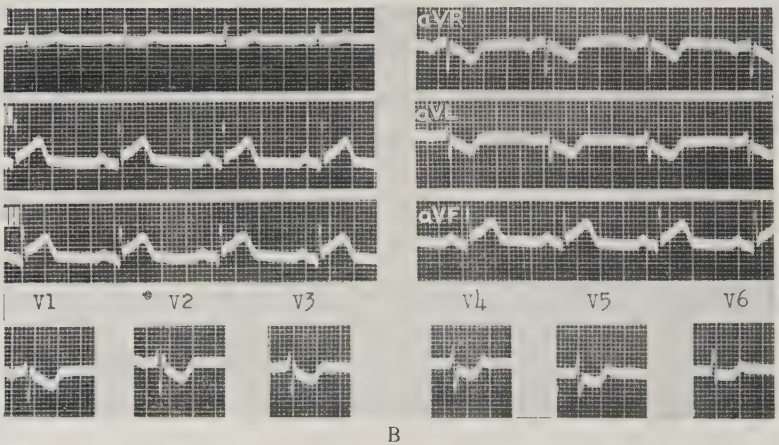
1. An abnormal QR occurs in leads V_1 and V_2; or in one or more of V_2, V_3 or V_4 with a normal initial R in V_1. A Q wave may be considered abnormal if it exceeds one quarter of the height of the following R wave or if it is prolonged more than 0.02 second from onset to nadir.
2. There may be an elevation of the RST segment in leads V_1 or V_2.
3. There are no abnormal Q waves in V_5 or V_6.

Standard limb leads usually show no significant abnormalities, as they are

perpendicular to the direction of the advancing excitation wave and current of injury.



A



B

Fig. 52. Posterior wall infarction. *A*. One half hour after onset. R-T elevations in leads II and III and R-T depressions in leads I and CF_4. Tall, broad T waves. Auricular fibrillation.

B. One day after onset. Same case. Sinus rhythm. Small Q_2 and Q_3 now present. R-T elevations in unipolar limb lead from left foot (aVF).

Rosenbaum et al.[135] suggested that some attacks of premonitory pain may actually represent small anteroseptal infarcts, which produce electrocardiographic changes only in the right precordial leads. The subsequent develop-

ment of classic symptoms and of classic electrocardiographic abnormalities in the standard limb leads and left precordial leads may be due to lateral extension of the anteroseptal infarct. If the entire septum is involved from anterior to posterior surface the electrocardiogram may disclose signs of anteroseptal infarction in precordial leads and of posterior infarction in standard leads.[134]

ANTEROLATERAL INFARCTION. When small infarcts are localized to the lateral portion of the anterior wall, the presence of a Q wave and associated abnormalities in the RST segment and T wave might be limited to precordial leads taken from the fourth, fifth and sixth positions and be absent in positions further to the right.

Lateral Wall Infarction (postero-lateral, apical-lateral, basal-lateral, and high lateral). Wood, Wolferth and Bellet[179] described electrocardiographic changes which they believed were associated with infarction of the lateral wall of the left ventricle. These consisted of depression of RST in leads I and II, absence of signs of infarction in lead III and depression of RST in lead IV.

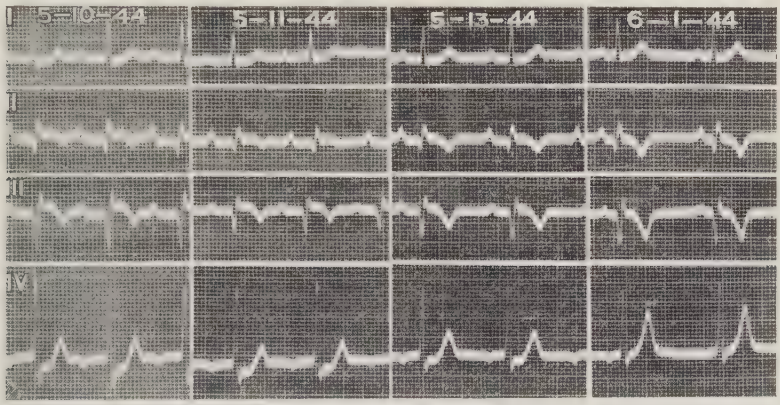


Fig. 53. Posterior wall infarction. Progressive changes.

Thomson and Feil[164] found 19 cases of infarction of the lateral wall (9 recent) in 106 necropsied cases of cardiac infarction. In 4 of the 9 recent cases the electrocardiogram presented a pattern resembling that described by Wood et al.[179] On the other hand, Shaffer[146] could not verify these findings in 5 cases of recent uncomplicated infarction of the lateral surface of the left ventricle. In these cases the electrocardiogram disclosed either mixtures of the patterns associated with anterior and posterior infarction or changes characteristic of one or the other.

In 6 cases of suspected infarction of the basal position of the lateral wall of the left ventricle, Rosenbaum, Wilson and Johnston[136] found no unequivocal evidence of infarction in the standard precordial leads. However, distinctive changes were observed in unipolar leads from points on the lateral surface of the upper left thorax. In another study of 105 cases showing lateral wall infarction at autopsy, Myers et al.[111] discovered electrocardiographic changes in one group like those described under anterolateral infarction. In another group of cases representing a lateral extension of a posterior infarct, the diagnosis of lateral extension could be made from V_6 or V_L and of posterior infarction from standard leads and V_F. Primary lateral infarcts near the apex revealed abnormalities in V_5, V_6 and V_L; those near the base disclosed abnormalities

in V_L and leads high in the left lateral thorax but uncommonly in V_5 or V_6. Q waves are most significant, while RST elevations or depressions depend on the subepicardial or subendocardial localizations of the infarct.

Posterior Wall Infarction (Q_3-T_3 Pattern). 1. There is an *early elevation of the ST segment in lead III and usually also in lead II.* At the same time the ST segment in lead I is depressed (discordant ST deviation) (Fig. 52).

2. The ST_3 elevation has a characteristic upward convexity or dome shape, beginning at its high take-off from the R wave and sloping downward toward the T wave (Fig. 53).

3. *The T wave in lead III and usually also in lead II becomes progressively lower, diphasic and eventually sharply inverted and* **V** *shaped.* The T wave in lead I is upright and often sharply pointed (Fig. 53).

4. There is often an *early appearance of a conspicuous Q wave in lead III and often also a smaller Q wave in lead II.* The Q wave in lead III may be the sole initial ventricular deflection or there may be a small R or small R and S waves. In lead II, Q, R and S are often all of small amplitude, producing a **W** or **M** shaped configuration. A similar configuration in lead III is usually not significant. There may be a tendency to left deviation of the electrical axis. The presence of a Q_3 and inverted T_3 in themselves may not signify myocardial infarction, for they may be produced by a transverse position of the heart. The significance of a Q_3 is enhanced if S is absent in lead I.[165] The presence of a deep Q wave in V_F strongly increases the probability that the Q_3 is due to posterior infarction, and not to a semitransverse or transverse position of the heart[114] (Fig. 52B). Left ventricular hypertrophy may produce a Q wave and inversion of T in V_F.[97a]

The *precordial leads* in cases of posterial wall infarction are not usually of diagnostic importance. The following abnormalities may be observed:

1. Early and transient depression of the ST segment. This is not as prominent as the elevation observed in instances of anterior infarction.

2. An extremely *tall T wave* may appear (above 12 mm.). An esophageal lead at the level of the ventricles may disclose more striking changes including presence of a Q wave, RST elevation, and T wave inversion.[118]

Combined Anterior and Posterior Infarction. In combined infarcts of the anterior and posterior walls of the left ventricle the electrocardiogram may disclose patterns which include elements of the Q_1-T_1 and of the Q_3-T_3 type, or changes representing defective intraventricular conduction or bundle branch block, or nonspecific QRS and T wave changes. Occasionally one observes at the onset changes suggestive of a posterior wall infarction with subsequent development of a pattern of anterior wall infarction, or vice versa. When there is an old infarct on one surface and a fresh infarct on the other, the changes due to the recent infarct may be added to or may replace those of the previous infarctions. Thus Q waves in leads II and III may be residua of an old posterior infarct, while RST changes with subsequent inversion of the T wave in lead I result from a recent anterior infarct. The standard leads may disclose the Q_3-T_3 pattern of a posterior infarct while the precordial leads reveal the additional presence of an anterior infarct. The V_F lead may be helpful.[112a]

Acute Myocardial Infarction with Bundle Branch Block. This usually occurs with extensive septal infarction. In left bundle branch block, the left ventricular cavity remains positive until the impulse from the right bundle branch crosses the septum. The usual Q wave due to transmission of left subendocardial nega-

tivity to the exploring electrode over an infarct does not occur because of the positive left endocardial potential. An exception is a complete left to right infarction of the septum whereby the right cavity negative potential is transmitted immediately through inert tissue to the left.

With *left bundle branch block,* the diagnosis of myocardial infarction is usually precluded except with extensive septal infarction.[173]

With *right bundle branch block,* and a *posterior wall infarct,* the characteristic electrocardiographic changes of the latter may be visible in the limb leads, while the right bundle branch pattern is most distinctive in right precordial leads.

With *right bundle branch block* and an *anterior wall infarct,* the presence of the latter may be obscured in the standard limb leads but revealed clearly in

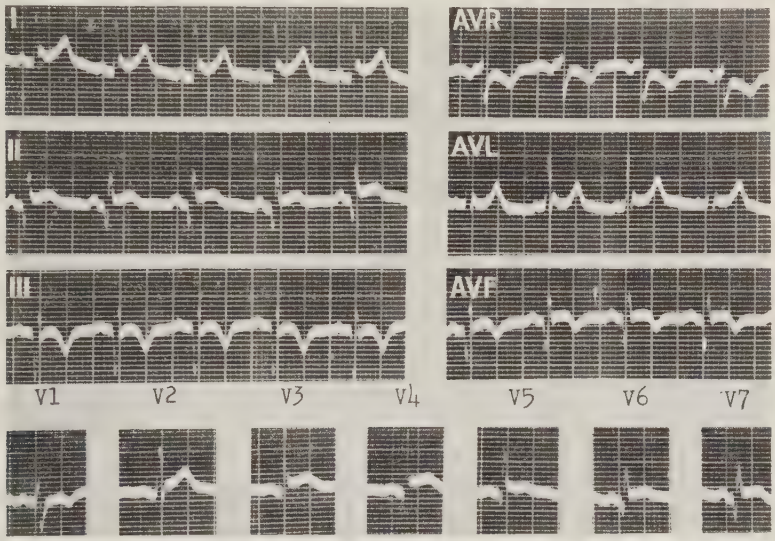


Fig. 54. Acute posterior wall infarction with pericarditis. R-T elevation in leads II, III and AVF, with characteristic convexity upward. Cove-plane T wave inversion and Q waves in leads III and AVF indicate posterior infarction. The R-T elevations with concavity upward in lead I and in precordial leads without Q waves suggest pericarditis.

the precordial leads, which disclose the classic Q wave, RST elevation and T wave inversion (Fig. 51).

Sometimes bundle branch block in the course of acute myocardial infarction is of transient duration. Serial electrocardiograms may then disclose the characteristic changes of acute infarction in both the limb and precordial leads at those times when bundle branch block is not present. Occasionally, when the electrocardiographic changes of acute myocardial infarction are obscured by those of bundle branch block, there may be sporadic interpolated premature ventricular beats which reveal characteristic changes of infarction.[44]

In cases of acute myocardial infarction with diffuse pericarditis, both the pericarditis and cardiac infarction may produce distinctive changes (Fig. 54). A differentiation between the electrocardiographic alterations of pericarditis and acute myocardial infarction is discussed later (p. 468).

Less Specific Electrocardiographic Changes. Dressler[43] has noted that at certain stages of acute myocardial infarction and sometimes during the period

of preliminary pain, an electrocardiographic pattern in which T_1 is lower than T_3 is indicative of an anterior wall infarction. This is especially significant when the patient is over forty years of age and has been subject to attacks of angina pectoris. In young persons rheumatic heart disease is more commonly responsible for this picture. Normally T_1 is taller than T_3 except when the heart has a vertical position, when there is pulmonary emphysema, or rarely in the presence of congenital heart disease, thyrotoxicosis, uremia, vitamin deficiency and trichinosis. This pattern, in which T_1 is smaller than T_3, is also associated with an old myocardial infarct. Consequently a consideration of the clinical history is essential to determine whether this pattern signifies recent or old cardiac infarction.

Characteristic elevation of the RST segment with inversion of the T wave in lead I is strongly suggestive of anterior wall infarction even when the classic reciprocal RST depression in lead III is absent or inconspicuous. Similarly in cases of anterior wall infarction, the RST segment elevation in lead I may be inconspicuous or absent and T_1 may be only flattened or isoelectric, but the reciprocal ST depressions and prominence of the T waves in leads III and II may be striking. Sharply inverted **V** shaped T waves may rarely appear in the standard leads after acute myocardial infarction, but these findings in themselves are not diagnostic of the infarct.

In some cases the significant finding is the low voltage (less than 0.5 mv. or 5 mm.) of the QRS complex in all leads with or without inverted T waves. Often the QRS complexes are not only of low voltage but slurred and notched, and they may be widened beyond the normal limit of 0.1 second. These findings are associated with both fresh and old infarction as well as other conditions,[156] but in some instances with the aid of the clinical history and previous electrocardiograms it may be possible to conclude that the infarct developed recently. Similar significance may be attached to an **M** or **W** shaped QRS of low voltage in leads I or II when interpreted in the light of clinical data.

The P wave may be increased in amplitude and occasionally it is notched and widened. Master[101] observed a P wave of 2 mm. or more in at least one lead (usually lead II or leads I and II) in 40 per cent of his cases of acute coronary occlusion, and attributed it to enlargement of the left atrium. Bloom and Gilbert[20] observed a higher incidence of arrhythmias and conduction disturbances in those cases with large or notched P waves than in those with normal P waves. The occurrence of conduction disturbances and arrhythmias in the electrocardiograms seen after acute myocardial infarction is discussed below.

Cardiac Arrhythmias in Acute Myocardial Infarction

Premature contractions (extrasystoles), usually of ventricular origin, constitute the most frequent arrhythmia associated with acute myocardial infarction. Rarely, multiple premature ventricular contractions presage the onset of ventricular tachycardia (see below).

All other arrhythmias combined appear much less often than premature contractions, perhaps in about 15 to 20 per cent of cases of acute myocardial infarction. They usually develop in the first three days of the attack, but in occasional cases at any other time in the first two weeks. Most of the arrhythmias subside spontaneously in four to twenty-four hours.

Auricular fibrillation is next in frequency to premature ventricular contrac-

tions, while auricular flutter is observed very uncommonly. Auricular fibrillation often appears in the first few days and disappears spontaneously after several hours. For this reason it is easily overlooked. Occasionally, however, one of these paroxysms is the onset of persistent auricular fibrillation.

Auricular or nodal tachycardia has been encountered in 0.5 to 2.0 per cent of cases.[4a] It may persist for several weeks.

Ventricular tachycardia occurs rarely but may preface ventricular fibrillation and death. For this reason, its prompt recognition and treatment are essential (p. 285).

Various grades of *heart block* are not infrequent. The *prolongation of the P-R interval* was observed by Master et al.[102] in 16 per cent of 375 cases of acute myocardial infarction. In addition, partial and complete heart block were noted in 3.2 per cent of their cases. Bean[14] observed a P-R interval of 0.2 second or longer in 30 per cent of his cases. The prolongation of the P-R interval appears early, usually in the first week and often on the first or second day of the attack. However, occasionally it is observed only after several weeks. Decided variations in the length of the P-R interval may suggest that the process in the heart muscle is both recent and active. Bundle branch block and other intraventricular conduction disturbances are found more frequently in cases of cardiac infarction with a prolonged P-R interval than in those with a normal P-R interval. Usually the prolongation of the P-R interval persists several weeks and disappears. Occasionally it remains permanently, differing in this respect from other arrhythmias which rarely persist after myocardial infarction.

Partial heart block with Wenckebach periods and dropped beats occurs occasionally. Both partial and complete heart block occur early in the attack and they may represent the first or only indication of an acute coronary occlusion. *Complete heart block* with auriculoventricular dissociation has been considered very uncommon, but Schwartz[141] reported personal observation of the surprisingly large number of 15 cases. According to Kerr,[83] complete heart block occurs in only 2 to 3 per cent of cases of acute cardiac infarction and all forms of conduction disturbance in 7 to 8 per cent. As a rule, heart block occurs very early in the attack. It is usually persistent but may disappear. The occurrence of heart block is almost always associated with occlusion of the right coronary artery,[6] which in 90 per cent of hearts supplies the a-v node and the bundle of His through its ramus septi fibrosi. Since this branch arises almost at the origin of the right coronary artery, proximal to the usual site of thrombosis, the blood supply through this vessel to the node and bundle of His is only infrequently suppressed.[150] Because of a rich anastomosis between the left and right coronary arteries in the region of the a-v node and bundle, complete heart block is most likely to develop when both arteries have beer occluded. In most cases of heart block, autopsy examinations reveal multiple coronary occlusion with massive cardiac infarction, usually involving the interventricular septum. As a result, impaired intraventricular conduction (as denoted by wide and notched QRS complexes) is often associated with complete heart block.[141] Sometimes complete heart block is the result of damage and interruption of both bundle branches and not of the main bundle of His.

The *Adams-Stokes syndrome* (p. 302), characterized by convulsions, syncopal attacks and coma, may appear after the development of complete heart block,[141] but usually only when the ventricular rate falls below 40. Thus the

incidence of the Adams-Stokes syndrome after acute myocardial infarction is much lower than that of complete heart block. Cookson[33] observed 5 cases of syncope or convulsions in the course of 200 cases of acute cardiac infarction. Two had syncope and 3 the complete Adams-Stokes syndrome, including convulsions. In one instance an electrocardiogram taken during the attack showed complete heart block with the rate falling from 100 to 34. These attacks may also result from periods of ventricular tachycardia or ventricular flutter and fibrillation, which culminate in ineffectual cardiac systole and consequent cerebral ischemia. In some instances, paroxysms of Adams-Stokes syndrome result from ventricular standstill following supraventricular or ventricular tachycardia or partial heart block. In cases with Adams-Stokes syndrome complicating cardiac infarction, other abnormal rhythms are common between attacks. Cookson[33] found posterior ventricular infarction in 4 of 5 cases of this type; in the other the site of infarction was undetermined.

Bundle branch block and other intraventricular conduction defects (p. 306) are fairly common, but only recognizable electrocardiographically. These disturbances usually appear early and persist. However, I have seen bundle branch block appear with the onset of acute myocardial infarction and disappear as the more classic cardiographic features of this condition emerged. But when the bundle branch block persists, it often obscures the electrocardiographic features of myocardial infarction. Intraventricular and auriculoventricular conduction defects may be associated.

COMPLICATIONS AND CAUSES OF DEATH[145]

Shock and *acute left ventricular failure* occur so frequently with acute myocardial infarction that they have been discussed as intrinsic features of the disease rather than as complications. Either of these may be sufficiently severe to cause death within the first few days after the onset.

Chronic left ventricular failure may develop gradually weeks or months after the occurrence of acute myocardial infarction. Under these circumstances it is characterized by recurrent episodes of nocturnal dyspnea, a progressively increasing dyspnea on exertion, orthopnea, cough and the presence of râles at the bases of the lungs. Death may result from an acute attack of pulmonary edema. Often the symptoms of acute left ventricular failure subside after the first few days or weeks. In many cases chronic left ventricular failure persists for several years and the patient eventually succumbs to increasing left- and right-sided congestive heart failure or some other complication.

Right ventricular failure characterized by hepatic enlargement and tenderness, systemic venous engorgement and eventually peripheral edema may appear after the acute symptoms of myocardial infarction have subsided. If the acute infarction is not the first, these symptoms of right ventricular failure may appear from the outset. Patients with these symptoms may run a slow downhill course or die more or less suddenly from acute coronary insufficiency[91] or some other complication. Together, left and right ventricular failure with or without shock constitute the chief cause of death from acute myocardial infarction.[51]

Embolization. Visceral and peripheral embolism constitute the next most common cause of death, although such emboli are not always fatal.[28] Garvin[62] observed that in about 60 per cent of the cases of myocardial infarction that he studied, there were one or more infarcts (presumably due to embolism) in

the lungs, brain, kidneys, spleen, extremities and/or intestine. In a recent review of cases reported in the literature, Hellerstein and Martin[74] found an average of 11.5 per cent of embolism or infarction. In their own autopsy series of 160 cases 73 or 45 per cent were associated with embolism, which was the main cause of death in 12 per cent and a contributory cause in an additional 15 per cent. The frequency and importance of thromboembolic lesions in acute myocardial infarction has gained increasing significance recently because of the possibility of treatment with anticoagulants and surgery.

Pulmonary Embolism. Pulmonary embolism is the most frequent of these embolic complications of acute myocardial infarction and is a commoner cause of death than is generally recognized. Eppinger and Kennedy[51] found pulmonary emboli in 23 per cent of 200 cases of myocardial infarction proved at autopsy and emphasized the significance of pulmonary embolism as a cause of death. Massive pulmonary embolism accounted for 10 per cent of 577 deaths in somewhat more than 1000 cases of acute coronary occlusion studied by various observers.[115, 74] As a rule, pulmonary emboli originate from peripheral thrombi in the veins of the lower extremities,[15] unlike the other forms of emboli which originate in mural thrombi in the left ventricle or atrium.

Thus pulmonary emboli may be only in part a direct consequence of the cardiac infarction and slowing of the peripheral circulation; bed rest and the associated venous stasis are probably more important causes. This consideration is important in the treatment of acute myocardial infarction. Although mural thrombi associated with myocardial infarction are located almost always in the left ventricle, they may also form in the right ventricle when there is extensive infarction of the interventricular septum. In the latter circumstance the pulmonary emboli may be generated from a mural thrombus, but this is a much less frequent source than the peripheral veins, and the resulting emboli are less likely to be as large or as serious. In still other cases, in which there is marked cardiac dilatation associated with right-sided heart failure, mural thrombi may develop in the right auricle and may promote pulmonary emboli.

Pulmonary embolization may occur within the first few days after the onset of myocardial infarction, but usually not until the end of the first week, or during the second week of the disease. The emboli tend to recur, each new embolus increasing the probability of a fatal outcome. These episodes of recurrent emboli are usually misinterpreted as repeated fresh coronary thromboses. Pulmonary embolization may occur while the patient is still bedridden, but frequently it develops suddenly when the patient sits up in bed, strains at stool or gets out of bed for the first time.

Cerebral emboli are probably the next most serious form of embolization and, like other emboli to the systemic arteries, originate in left ventricular mural thrombi. Conner and Holt[31] reported the development of cerebral embolism in 14 (5 per cent) of their 247 cases, while Dozzi[41] in reviewing a series of 1000 consecutive necropsies found that in 12 (29 per cent) of 41 cases of coronary thrombosis there was an associated cerebral vascular accident. Cerebral infarction was found in 5 to 15 per cent of various series of cases of myocardial infarction proven at autopsy.[15, 62, 74] The clinical features which cerebral emboli may produce and the possibility that these manifestations may overshadow or obscure the more classic features of myocardial infarction have already been discussed (p. 434). Cerebral emboli usually result in encephalomalacia which may be evidenced by aphasia, hemiplegia, convulsions and psychic

disturbances, while the underlying myocardial infarction is unsuspected.[42] Occasionally such emboli are responsible for or contribute materially to the fatal outcome.

Visceral emboli usually affect the kidney and spleen and occasionally the intestinal tract. They may produce renal infarction, with or without lumbar and ureteral pain and hematuria; splenic infarction, usually asymptomatic but sometimes denoted by local pain on respiration and a splenic rub due to perisplenitis; and rarely intestinal infarction with acute abdominal symptoms.

Peripheral Emboli. Embolization of the aorta at its bifurcation (saddle embolus), of the iliacs, of the popliteals and of other peripheral arteries has also been noted. Usually the embolus lodges at the bifurcation of a peripheral artery. The most common site is the femoral at the origin of the profunda femoris, and next most common are the common iliac, axillary and brachial, popliteal and aorta in that order.[119] Peripheral embolism is characterized usually by acute and excruciating pain, blanching of the affected area of skin, loss of sensation, coldness of the extremity, loss of arterial pulsation and later loss of motion of the affected muscles. Eventually these emboli may result in gangrene of the extremity, but when located distally in the lower extremity or in any artery of the upper extremity, an adequate collateral circulation usually precludes the occurrence of gangrene.

Bronchopneumonia. The true incidence of this frequent complication of acute myocardial infarction is difficult to determine. On the one hand it is unrecognized when it complicates advanced pulmonary congestion associated with râles at the bases of the lungs; on the other hand it is often diagnosed clinically when the pulmonary signs and other clinical features are actually due to pulmonary embolism with infarction. Undoubtedly pulmonary congestion, pulmonary infarction and bronchopneumonia are often combined in the same person. Bronchopneumonia is commonly a terminal or terminating incident in fatal cases.

Rupture of the Heart. This is one of the commoner causes of sudden death in the first few weeks after acute myocardial infarction.[16, 50, 40] Martland[99] found a rupture of the heart in 2 per cent of 2000 cases investigated by the medical examiner; these comprised about 7 per cent of the 318 cases of coronary occlusion in his series. While cardiac infarction due to coronary arteriosclerosis and occlusion is by far the commonest cause of rupture of the heart, the latter may also result rarely from bacterial endocarditis, myocardial abscess due to sepsis, dissecting aneurysm of the sinus of Valsalva, gummatous (syphilitic) myocarditis, tuberculous perimyocarditis, echinococcus cyst and malignancy. Traumatic rupture of the heart is discussed in Chapter 44.

According to Fulton,[59] one eighth of the patients who succumb in the first three weeks after acute myocardial infarction die from rupture of the heart. Krumbhaar and Crowell[86] found the cardiac rupture through the left ventricle in 225 cases and through the right in 32. The anterior surface was lacerated three times as often as the posterior surface. Infarction and rupture of the right atrium have also been reported (p. 461).

Rupture of the heart results from a through and through laceration of an infarcted area which is still soft and necrotic. The rupture occurs most frequently in the first week, sometimes in the second week, and rarely thereafter. In Fulton's series,[59] death from cardiac rupture occurred within seventeen days in all but one and the average was nine days after cardiac infarction.

It may occur in the first two or three days. While softening of the myocardium is a major factor responsible for ventricular rupture, the height of the intraventricular pressure may also be important. Edmondson and Hoxie[50] found that patients who have hypertension which persists after infarction are three times more likely to develop cardiac rupture than those who have normal or subnormal blood pressures. Although cardiac rupture may occur when the patient is in bed, occasionally a specific physical strain or continued normal activity after the myocardial infarction may contribute to the cardiac perforation. Thus while Friedman and White[58] encountered 10 cases of rupture of the heart (9.4 per cent) in 105 autopsied cases of myocardial infarction in a large general hospital, Jetter and White[77] found 16 instances of rupture of the heart (73 per cent) out of a total of 22 autopsied cases of acute myocardial infarction in mental institutions. The implication was that continued activity by mental patients with unrecognized myocardial infarction was an important factor in causing rupture of the heart.

Rupture of the heart following cardiac infarction leads to hemopericardium, cardiac tamponade and sudden death. Occasionally the amount of blood in the pericardium may even exceed a liter, but usually about 250 cc. is sufficient to cause cardiac tamponade. Death may occur within a few minutes after the rupture, but occasionally there is a survival period of a half hour or longer.

Rupture of the Interventricular Septum. Rupture of the interventricular septum after infarction of this portion of the myocardium is less common than that of the ventricular wall.[170, 176] Edmondson and Hoxie[50] observed 13 instances of rupture of the interventricular septum compared with 56 of the left or right ventricle. The perforation is usually a single one in the lower or central portion of the septum varying from pinpoint size to 6 cm. in length; occasionally there are 2 or 3 perforations.

Unlike ventricular rupture, rupture of the septum can be readily diagnosed ante mortem,[138, 170, 176] and may occasionally permit a period of survival of several months[109] or even up to five years.[178] Clinically the symptoms are those of severe myocardial infarction associated with intense dyspnea and increasing shock. The symptoms and signs of right-sided heart failure may develop rapidly. The diagnostic feature is a loud and often roaring systolic murmur which is usually loudest in the fourth and fifth interspace near the left border of the sternum. A systolic thrill is almost always present in the same region, but it may be absent. The prognosis is almost always extremely poor, partly because the infarction in these cases is usually extensive and partly because of the added circulatory disturbance of the acute perforation itself. In those who survive, even for a few months, there are usually symptoms and signs of left- and right-sided congestive failure.

Rupture of a papillary muscle is a rare complication of cardiac infarction.[157, 110, 38] It may be due also to bacterial endocarditis or trauma. The posterior papillary muscle of the left ventricle is most often affected, the anterior papillary muscle is next in frequency and, rarely, the papillary muscles of the right ventricle. Sometimes there are no auscultatory findings, but there may be a loud apical systolic murmur, or a whistling to and fro murmur, or a murmur and a thrill resembling those of a ruptured interventricular septum.[166]

Sudden Death. Sudden or unexpected death is a common termination of acute myocardial infarction. It may be the only manifestation of the attack (p. 432) or it may occur in any stage of the acute disease during convalescence.

Among its causes massive pulmonary embolism and rupture of the heart have already been mentioned. It is believed that most often sudden death results from ventricular fibrillation, although only rarely is it possible to demonstrate this electrocardiographically.[108, 163] In some instances, sudden death may result from cardiac standstill due to vagovagal reflexes from the infarcted heart muscle, as in a case observed by Goodrich and Needles[65] in which cardiac standstill followed ventricular tachycardia. Of 16 instances of sudden death associated with coronary disease, analyzed by Stroud and Feil,[160] 8 were due to a sudden paroxysm of ventricular fibrillation and 8 to sudden ventricular



Fig. 55. Left ventricular aneurysm due to old myocardial infarction. Localized bulge above cardiac apex which showed diminished pulsations by fluoroscopy and kymography.

standstill. In patients with complete heart block and Adams-Stokes syndrome following cardiac infarction, death may occur suddenly during a paroxysm of prolonged cardiac asystole. It may follow the intravenous administration of various therapeutic agents such as aminophylline, papaverine and quinidine.[130] A definite causal relationship between the drug and the fatality is usually difficult to establish since sudden death strikes so commonly in cases of acute myocardial infarction.

Aneurysm of the Left Ventricle. Aneurysm of the left ventricle is usually due to myocardial infarction although rarely it may result from congenital defects, trauma, myocardial abscess and ulcerating bacterial endocarditis. It is said to occur in 7 to 8 per cent of cases of cardiac infarction, but it is probably much more frequent.[155, 98, 126, 125, 45, 60, 28a] Applebaum and Nicolson[3] found ventricular aneurysm present in 57 (38 per cent) of 150 cases of coronary oc-

clusive disease. Inconspicuous aneurysms are easily overlooked at necropsy when the pouch is not distended with blood as it is during life.

Following coronary occlusion the intraventricular tension stretches the noncontracting infarcted heart muscle and may produce a localized bulge where the myocardium consists only of a relatively weak thin layer of soft necrotic muscle and fibrous tissue. This bulge, known as a ventricular aneurysm, may not protrude beyond the remaining surface of the ventricle except during systole, or it may be so prominent that it resembles a tumor.[7] It may be filled with thrombus; the overlying pericardium is usually adherent. Sometimes the aneurysm is partially calcified.[19] It may develop during the acute stage of infarction[97] and become more prominent after healing. But often it is first recognized months or years after the acute infarction. The wall of the aneurysm may be perforated, but almost always during the acute phase only.[59] The site of the aneurysm corresponds to the usual site of the infarcts at the apex and anterior wall of the left ventricle, or at the base and posterior wall.

Although there are no characteristic symptoms of ventricular aneurysm, angina pectoris may be associated and symptoms of congestive heart failure are common. Cerebral or other embolism may complicate endocardial thrombosis. Rarely it results in spontaneous rupture.[18] Physical examination may disclose a forceful and rather broad pulsation of the anterior chest wall at the level of the fifth rib or interspace, just inside the midclavicular line. This pulsation is often distinguishable from that of the apical impulse. The heart sounds are frequently muffled and gallop rhythm is common.

Roentgenologic examination[142] may disclose not only cardiac enlargement, but also a circumscribed bulge or hump in the lower left (ventricular) contour (Fig. 55) or a sharp angulation or ledge which transforms this contour into oblong shape. The aneurysm may be best visualized in the oblique positions.[153] Its shadow cannot be separated from the heart shadow in any position in which it is seen. Occasionally its demarcation is accentuated when lime salts have been deposited in its wall. Fluoroscopic or roentgenkymographic examination may reveal a paradoxical pulsation of the aneurysmal site, contrasting in direction with the pulsation of the remainder of the left ventricle, but this may be observed also after myocardial infarction without distinct aneurysm.

The electrocardiographic findings are those of old infarction of the anterior or posterior wall, bundle branch block or nonspecific evidences of myocardial damage. RST segment elevations and cove plane inversion of the T wave, ordinarily associated with acute myocardial infarction, may be observed with ventricular aneurysm when cavity potentials are transmitted through a completely fibrotic aneurysmal wall.[112] Goldberger and Schwartz[64] described electrocardiographic patterns of ventricular aneurysm in standard leads characterized by (1) small R_1 and deep S_2 and S_3 and (2) main deflection downward in the three standard leads due to unusual rotation of the heart.

The diagnosis of ventricular aneurysm may be based on a history or definite electrocardiographic demonstration of previous myocardial infarction and the finding of a strong abnormal precordial pulsation contrasting with a weak first sound at the cardiac apex.[95] The roentgenologic findings mentioned above may confirm this clinical diagnosis or suggest it independently.[34] A ventricular aneurysm must be differentiated roentgenologically from a tumor of the heart, a local pericardial effusion, pericardial cyst, aneurysm of the sinus of Valsalva, localized calcification of the pericardium, gumma of the myocardium, syphilitic

aneurysm of the descending aorta and enlarged pulmonary conus. In doubtful cases electrokymography and angiocardiography may be diagnostically helpful.

The outlook for patients with ventricular aneurysm[69] is that of the underlying disease, i. e., myocardial infarction (p. 475). Survival for ten years has been reported by Young and Schwedel.[182]

Periarthritis of the Shoulder and Other Skeletal Lesions. Pain, stiffness and marked limitation of motion of the shoulder joint, shoulder girdle and arm occasionally result from acute myocardial infarction.[49, 24, 52, 4] The symptomatology may vary from mild pain on motion with little or no limitation to severe pain with almost complete limitation of motion, especially of abduction and external rotation ("frozen shoulder"). Edeiken and Wolferth[49] reported 14 cases of persistent pain in the shoulder joint, usually developing coincidentally with, or within four weeks after acute myocardial infarction. In severe cases it may persist from six months to two years; usually it subsides spontaneously but it may recur.

Usually the left shoulder and arm are affected, but the right side or both sides may be involved. The predominance of the involvement of the left shoulder region suggests a causal relation to the distribution of the cardiac pain, because in patients without a history of angina pectoris or coronary thrombosis periarthritis of the right shoulder greatly exceeds that of the left. Furthermore, there is a tendency for the right shoulder to be affected when the pain of myocardial infarction radiates to the right side.[52]

This complication has usually been attributed to reflex spasm of the muscles and ligaments around the shoulder, secondary to cardiac pain impulses which are referred to the same segments of the spinal cord as innervate the affected muscles and ligaments. Boas and Levy[24] and Askey[4] suggested that these reflexes accentuated a previously existing but subclinical periarthritis. Ernstene and Kinell[52] attribute the complicating syndrome to protective disuse of the shoulder and abnormal tension under pain of the muscles of the shoulder girdle, and my own observations have led me to believe that disuse is at least an important contributory factor. This explanation accounts satisfactorily for the tendency to involvement of the shoulder to which the pain is referred, since this is the extremity which is favored and not used. Furthermore, periarthritis of the shoulder occurs very commonly, independent of cardiac pain, under a variety of circumstances which involve disuse and abnormal posture of the affected extremity.

Meyer and Binswanger[107] observed pain, stiffness, swelling and disability of the joints of the right hand and wrist following acute myocardial infarction in 3 patients whose pain during the attack had radiated chiefly down the right upper extremity. Prolonged disuse because of the pain was also invoked to account for this complication. Askey[4] observed pain, stiffness and swelling of the finger joints with glossy skin and purplish red discoloration in association with the shoulder pain. In some cases there developed a thickening of the palmar aponeurosis resembling the early stage of Dupuytren's contracture.[81] Because of the changes in the skin and the latter development, Askey[4] concluded that the syndrome was the result of sympathetic nerve disturbance caused by myocardial ischemia and preexisting shoulder and hand lesions. Trophic ulcers of the hand have been noted following myocardial infarction.[147] Johnson[78] noted disabling changes in the hands resembling sclerodactylia in 39 (21 per cent) of a series of 178 consecutive cases of acute myocardial infarction. He

attributed these changes to anoxia of the tissues of the fingers caused by reflex vasoconstriction induced by cardiac pain. But this explanation fails to account for the interval of three to sixteen weeks between the pain of the infarction and the development of the changes in the hands.

INFARCTION OF THE ATRIA

Infarction of the atria due to coronary artery occlusion has until recently been noted rarely in comparison with the frequency of ventricular infarcts. Bean[15] observed 2 atrial infarcts in a series of 287 cases of myocardial infarction and Feil et al.[54] 2 others in 34 cases of myocardial infarction. Recently, however, Cushing and associates[35] observed 31 instances of atrial infarction (17 per cent) in a series of 182 cases of myocardial infarction. In 6 of these the atrium alone was affected. Atrial infarction is easily overlooked on gross examination of the heart, but its presence may be suggested by the finding of atrial mural thrombi which occur in 80 per cent of the cases.[168] It is usually difficult to find an occlusion of the corresponding artery supplying the affected area, but extensive and severe arteriosclerosis or occlusion is usually present in the larger coronary arteries. The right atrium (especially the appendage) is involved much more frequently than the left and usually on its anterior surface.

Atrial infarction may result not only from coronary arteriosclerosis but also from periarteritis nodosa, and from less specific obliterating endarteritis of the small branches of the coronary arteries. It has also been noted in a case of an occluded congenital single coronary artery[133] and in cases of bacterial endocarditis with ulcerating lesions. In some instances hemorrhagic necrosis of the auricular wall resembling an infarct results from the perforation of a true or false aneurysm.

Rupture of the atrial wall may result from infarction. Of 710 cases of rupture of the heart collected by Krumbhaar and Crowell[86] and by Davenport,[36] 7 per cent involved the atria. Of 55 cases of atrial rupture collected by Clowe, Kellert and Gorham,[30] 39 were situated in the right atrium, 15 in the left, and 2 in the interatrial septum. Clowe et al. called attention to the high incidence of atrial rupture (47.7 per cent) before the age of forty, as compared to 6.7 per cent for ventricular rupture during this age period. The rupture of the atrium usually extends into the pericardium, producing hemopericardium, but occasionally it extends into the pleural cavity.

No distinctive clinical picture has yet been evolved for atrial infarction. In some of the cases reported, the symptoms and signs were indistinguishable from those due to ventricular myocardial infarction. In many instances, atrial infarction is combined with ventricular infarction and the clinical picture is that of the latter. Symptoms may first appear with rupture of the atria and may consist of shock and rapid death due to cardiac tamponade.

Recent interest in infarction of the cardiac atria has centered in efforts to associate this condition with a distinctive electrocardiographic picture. Abramson et al.[1] noted elevation of the P-Q segment in lead I on cauterization of the left atrium of dogs and cats, and depression of this segment on cauterization of either surface of the right atrium. Depressions of the P-T segments in leads II and III occur with similar injury to either atria. Langendorf[88] first described a case of infarction of the right atrium, in which characteristic electrocardiographic changes were noted. Young and Koenig[181] described deviations of the P-Q segment in 3 of their 4 cases of atrial infarction. However, Cushing et al.[35]

noted such P-Q abnormalities infrequently in their 31 cases. In the case of atrial infarction reported by Hellerstein[73] the diagnosis was made ante mortem on the basis of changing atrial mechanism, heart block, and elevation of $P\text{-}T_A$ segment in leads II and III (posterior wall atrial infarct).

The *diagnosis of atrial infarction* in cases of clinical myocardial infarction may be suggested by (1) atrial arrhythmias, especially if they change rapidly, including auricular fibrillation or flutter, atrial premature beats, nodal rhythm, sinus arrest; (2) elevation or depression of $P\text{-}T_A$ segment, especially depression, since most of the infarcts are anterior; (3) changing contour of the atrial T wave (T_A); (4) changing contour of the P waves; (5) atrioventricular block.[133, 73]

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21

ACUTE CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

Diagnosis, Differential Diagnosis, Prognosis and Treatment

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

In most cases of acute myocardial infarction, the diagnosis is relatively simple and may be ventured with reasonable certainty on the basis of the history and symptomatology alone.

Chest Pain Suggesting Cardiac Infarction. Severe oppressive pain over the lower sternum or more extensively over the precordium or anterior chest, lasting at least a half hour and not relieved by rest or nitrites, is sufficient to warrant a tentative diagnosis of acute myocardial infarction in the absence of some other obvious cause of the pain. Characteristic radiation of the pain to the neck, shoulders or arms confirms the likely origin of the pain in the heart. But unless other distinctive symptoms and signs of myocardial infarction appear, electrocardiographic confirmation is essential for definite diagnosis. Completely normal electrocardiograms, taken early and repeated frequently with multiple precordial leads, should cast extreme doubt on the diagnosis of a recent myocardial infarction.

The diagnosis of acute myocardial infarction should be suggested not only by the pain of the classic character and duration but also by the milder and more transient pain of angina pectoris when it occurs with increasing frequency, with less and less effort or at rest, or when it can no longer be relieved by nitrites.

Many collateral features may enhance the probability that an attack of severe prolonged chest pain is actually due to an acute myocardial infarction, but pain may be the only subjective complaint. Among the important associated symptoms are dyspnea, weakness, nausea and vomiting, and perspiration. The patient's extremities may feel cold and moist; his skin and mucous membranes may present an ashen cyanosis. A rapid fall of blood pressure within twenty-four hours or even a more gradual drop in the next few days is an important confirmatory sign. A moderate elevation of temperature and leukocytosis and an accelerated rate of sedimentation of erythrocytes are additional features supporting the diagnosis. In cases of infarction with mild symptoms an in-

creased sedimentation rate is especially valuable in provoking a search for further evidence of this condition.

It is important to emphasize that there may be no abnormal physical signs in the heart or lungs. But evidence of acute left ventricular failure varying from râles at the bases of the lungs to extensive signs of pulmonary edema, as well as the presence of gallop rhythm or a pericardial rub, may affirm the clinical diagnosis of myocardial infarction.

Shock, Syncope or Prostration Suggesting Acute Cardiac Infarction. Cardiac infarction should be considered when a person unexpectedly and without apparent cause experiences severe prostration or collapse, when he suffers an attack of syncope, or when he presents the clinical picture of shock. The patient or his family should be queried regarding the past history of angina pectoris, coronary occlusion, symptoms of heart failure, hypertension or diabetes. Specific questioning may expose the coexistence of an oppressive chest pain or the pain may appear when the patient recovers somewhat from his prostration or syncope. The underlying cardiac infarction may be attested in subsequent days by the development of fever, leukocytosis, increased sedimentation rate of red blood sells, gallop rhythm or a pericardial rub, and by symptoms and signs of left ventricular failure, and may be certified by characteristic electrocardiographic changes.

Acute Pulmonary Edema Suggesting Acute Cardiac Infarction. Every attack of acute pulmonary edema without obvious cause should be inspected as manifesting an acute cardiac infarction. As in the cases dominated by shock, careful questioning may reveal coexisting constricting sternal pain, which has been at least partially masked by acute dyspnea. The patient should be observed for a fall in blood pressure, and other confirmatory evidence of acute myocardial infarction.

Development or Intensification of Heart Failure Suggesting Acute Caridac Infarction. When a person begins to experience attacts of nocturnal dyspnea or dyspnea on the mildest exertion, or when a patient with such symptoms suddenly presents enlargement of the liver, engorgement of the peripheral veins or peripheral edema, the possibility of a recent cardiac infarction should be investigated. While occasionally the physician may discover a pericardial rub or gallop rhythm, a fall in blood pressure, fever or leukocytosis, usually these signs are absent. The diagnosis then depends essentially on the exposition of characteristic electrocardiographic changes. The electrocardiogram in this type of case having often been altered by a previous infarct, the fresh infarction may be documented only by changes in the QRS or T waves without the distinctive pattern of a primary acute cardiac infarct.

Other Symptoms Suggesting Acute Cardiac Infarction. Since in many cases of acute cardiac infarction chest pain may be mild, transient and easily forgotten and there may be no evidence of heart failure or shock, the diagnosis of acute cardiac infarction may sometimes be overlooked unless it is entertained whenever a person over forty presents symptoms not clearly attributable to other causes. The sudden and unexplained development of extreme fatigability or weakness, attacks of dizziness or syncope, indigestion, brief episodes of dyspnea and pallor or cyanosis, palpitation and a cardiac arrhythmia, or the occurrence of systemic embolization may each prove to have been due to an acute myocardial infarction. Frequent electrocardiographic examination is the only method of minimizing diagnostic oversight in this type of case. Special

attention is directed to the relative frequency with which cerebral vascular accidents are due to or associated with acute myocardial infarction and the necessity of routine electrocardiography to discover this association (p. 455). Similarly, unexplained postoperative fever, shock, or symptoms of cardiac failure often interpreted as direct complications of a surgical procedure may be found on electrocardiographic examination to be caused by cardiac infarction. The diagnostic value of routine preoperative electrocardiograms for control purposes appears obvious.

Electrocardiographic Diagnosis of Acute Cardiac Infarction. The electrocardiographic changes associated with acute myocardial infarction have been discussed in detail in a previous section, to which the reader is referred (p. 442). Although the diagnosis of acute myocardial infarction should be based on an appraisal of all the laboratory and clinical features as well as the electrocardiogram, certain electrocardiographic findings in themselves justify the diagnosis. In the absence of the classic clinical symptoms and signs of acute myocardial infarction, the relation of certain mild or nonspecific symptoms to cardiac infarction is sometimes betrayed only by electrocardiographic study.

Electrocardiographic Differential Diagnosis. Discordant RST elevations and depressions in leads I and III may be encountered in conditions causing advanced *left or right ventricular hypertrophy* and *left or right bundle branch block,* but in these cases the RST segment is elevated and concave upward in the lead in which T is upright and depressed in the lead in which T is inverted. Other features of the electrocardiogram of bundle branch block (p. 306) also help to distinguish it from that of acute myocardial infarction. The frequency with which bundle branch block conceals the electrocardiographic changes of acute myocardial infarction and the circumstances under which the latter may be recognized electrocardiographically when bundle branch block is present have been discussed (p. 450). In the precordial leads Q waves and elevation or depression of the RST segment may be due occasionally to left or right ventricular hypertrophy or dilatation.[75a]

Acute pericarditis like acute myocardial infarction may be documented in in its early stages by RST elevations. But the RST segment elevations in acute pericarditis are concordant, i. e., they occur simultaneously in leads I and III (and usually also in lead II) (p. 511), while those in myocardial infarction are discordant, i. e., an elevated RST in lead I is associated with a depression in lead III and vice versa. The RST elevation in acute pericarditis, like that in acute myocardial infarction, may appear only in lead I or leads I and II, while the RST segment in lead III is isoelectric. A distinction may still be made by the fact that the elevated RST segment in acute pericarditis is either concave upward or horizontal to the crest of the T wave, while it is usually convex upward in cases of acute myocardial infarction. The Q waves, seen in lead I and in the precordial lead after anterior wall infarction, or in leads II and III with posterior wall infarction, do not occur with acute pericarditis alone.

Electrocardiographic differentiation may be especially difficult when cardiac infarction is complicated by acute pericarditis as it is in at least 20 per cent of cases. The combination of infarction with pericarditis is suggested by the presence of concordant ST elevations as in isolated acute pericarditis, in association with Q waves in lead I and the precordial leads or in leads II and III.[9] The combination may also be revealed by transient concordant RST elevations as in pericarditis with subsequent discordant elevations and depressions in leads I and III as in myocardial infarction.

Massive pulmonary embolism (acute cor pulmonale) may produce electrocardiographic changes suggestive of *posterior* wall infarction (p. 877). Usually the electrocardiographic pattern of massive pulmonary embolism may be differentiated by the presence of a prominent S_1, a tendency to right axis deviation, a low origin of the T wave in leads I and II with a staircase ascent of ST_1 or $_2$ and frequent inversion of the T wave in the precordial lead, abnormalities not seen with posterior wall infarction. Furthermore, the T wave inversions in leads II and III appear within twelve hours after the onset while those associated with posterior wall infarction appear considerably later.

Digitalis may produce electrocardiographic changes which may obscure those of acute myocardial infarction. If the latter diagnosis is suspected but uncertain, electrocardiograms should be made if possible before administering digitalis. Usually digitalis causes a depression of the RST segment and inversion of the T wave in all leads. These changes should not be confused with those of acute myocardial infarction, but they may modify and obscure the characteristic RST segment elevations and T wave inversions associated with the latter. Occasionally digitalis produces electrocardiographic changes which may be confused with those of posterior wall infarction, namely an RST elevation in lead III and an RST depression in lead I (and lead II), in electrocardiograms which previously showed left axis deviation. A differentiation can usually be made by the presence of Q waves in leads II and III in cases of posterior wall infarction, and by the upward convexity of the elevated R-T segment in the former, as contrasted with the upward concavity of the elevated R-T segment due to digitalis. The Q-T interval is frequently shortened by digitalis and lengthened after acute cardiac infarction, but this is not a dependable distinction.

A *transverse position* of the heart may be associated with a large Q and inversion of the T wave in lead III. These findings may be misinterpreted as indicating a posterior wall infarction if the electrocardiogram was made because of nonspecific abdominal or chest discomfort. The Q_2 often present with myocardial infarction does not appear as a result of the transposition alone. The Q_3 wave due to position may disappear and the T wave become upright in an electrocardiogram taken with the patient upright and the lungs in deep inspiration. By the analysis of unipolar limb leads the Q and T changes may be revealed as the effect of the position of the heart and not of myocardial infarction. When Q_3 is due to posterior wall infarction, aV_F, the augmented unipolar left foot lead, almost always presents a Q wave which is 25 per cent or more of the R wave; when the Q_3 wave is due to transverse or semi-transverse position of the heart, a significant Q wave does not appear in aV_F.[76] Esophageal leads, at the ventricular level, also reveal characteristic Q wave changes in the cases due to posterior infarction.[78] In themselves, Q_3-T_3 changes are insufficient for a diagnosis of posterior wall infarction unless fortified by the characteristic RST elevation and subsequent serial changes or by the clinical history and findings.

DIFFERENTIAL DIAGNOSIS

Formerly any consideration of the differential diagnosis of acute myocardial infarction was apt to emphasize the frequency with which this condition was overlooked and mistaken for a variety of other conditions. In recent years increased knowledge of the features of acute myocardial infarction, a general awareness of its common occurrence and the widespread use of the electro-

cardiograph, often with exaggerated interpretations of minor or nonspecific changes, have led to the opposite tendency of erroneously diagnosing numerous other conditions as instances of acute myocardial infarction.[38] In differentiating between cardiac infarction and the following diseases, the physician must be alert to the possibility of error in either direction.

The variety of conditions which may have to be distinguished from acute cardiac infarction is so great that only a few which frequently perplex or are of special interest can be discussed in detail. However, in general, careful regard to the previous history, and to the details of the present illness, a complete physical examination, including in dubious cases roentgenologic examination of the chest, and study of the electrocardiograms, blood count and sedimentation time will resolve most ambiguities. In the absence of definite electrocardiographic confirmation of an acute myocardial infarction, preferably by serial tracings, systematic investigation should be made to determine whether some other disease accounts for the patient's symptoms.

Angina Pectoris

The pain of acute myocardial infarction is distinguished from that of angina pectoris by its longer duration (more than thirty minutes and usually for hours), its persistence with the patient at rest if it began during exertion, its failure to respond to nitroglycerin (but trial of this drug is rarely necessary for the differentiation). It is also distinguished by its frequent association with dyspnea or other evidences of heart failure, a fall in blood pressure and other evidences of shock, and by the development of fever and leukocytosis and an increased sedimentation rate. When pain is the only symptom of acute myocardial infarction, especially when the pain is relatively mild and not very prolonged, it may be difficult to distinguish cardiac infarction from angina pectoris. In such instances definite differentiation can be made only by repeated examinations of electrocardiograms, temperature, blood count and sedimentation rate. It should be reemphasized that paroxysms of angina pectoris which occur at rest after having previously occurred only on effort, or suddenly increase in severity and frequency, may actually represent attacks of myocardial infarction, to be discovered only by objective clinical laboratory and electrocardiographic examination. Attention has been directed (p. 402) to those cases termed "coronary insufficiency" or "coronary failure," in which the pain is intermediate in duration and severity between that of angina pectoris and myocardial infarction and not relieved by nitroglycerin. In these cases fever, leukocytosis and increased sedimentation rate are absent and the electrocardiogram shows only transient, reversible RST segment depressions or T wave changes.

Electrocardiograms taken during an attack of angina pectoris may disclose concordant RST depressions and occasional T wave inversions in the standard and in the precordial leads, which, however, are transient (p. 356). Wilson and Johnston[109] have noted in 5 cases of angina pectoris electrocardiographic changes similar in character and magnitude to those produced by myocardial infarction. As a rule there were deep S waves and pronounced ST depressions in leads II and III with occasional T wave inversion during the attack of spontaneous or induced pain. But these changes disappeared rapidly. In one there was discordant RST elevation in leads II and III with depression in lead I, transiently during the pain. When such changes persist after subsidence of

the pain or progress through the stages described for acute myocardial infarction, one should question the diagnosis of angina pectoris. When a patient happens to experience a transient attack of anginal pain during the recording of an electrocardiogram, the interpretation of conspicuous electrocardiographic abnormalities should be deferred until another record is taken an hour or more after the pain subsides. Since many patients with angina pectoris have suffered previous myocardial infarcts, their electrocardiograms may disclose evidences of intraventricular conduction defects and Q and T wave changes due to the old infarcts. Concordant ST depressions and T wave inversions, such as occur during attacks of angina pectoris, may also denote extensive subendocardial infarction.

Diseases of the Chest

Pulmonary Embolism. Pulmonary embolism, which occurs much more commonly than is generally supposed, is either entirely overlooked or is often misinterpreted as acute myocardial infarction. When manifested by chest pain, hemoptysis and physical signs in the lung, pulmonary embolism is easily diagnosed, but hemoptysis and physical signs are more often absent than not. In general, pain excited by pulmonary embolism is apt to be sharp and pleuritic in quality or to consist of an indefinite oppression of the chest, rarely displaying the typical localization and radiation of the pain of myocardial infarction. Cyanosis is often more striking and tachypnea more frequent than in cases of acute myocardial infarction. But in most instances the differentiation depends on the presence or absence of the characteristic electrocardiographic changes associated with myocardial infarction.

Cardiac Arrhythmias. The sudden advent of an arrhythmia, especially when associated with tachycardia, is sometimes attended by oppressive substernal pain which may be prolonged, palpitation, angor animi, cold sweat, and occasionally by dyspnea and other evidences of heart failure. Such a picture is often mistaken for acute myocardial infarction. Discovery of the arrhythmia either by clinical or electrocardiographic examination does not always exclude an acute myocardial infarct since the latter may be associated with certain arrhythmias at its onset. Cessation of the pain and other symptoms when the arrhythmia disappears, and absence of the characteristic electrocardiographic changes of cardiac infarction in subsequent records, exclude this condition. However, electrocardiographic changes resembling those of posterior myocardial infarction have been noted after cessation of a paroxysmal auricular tachycardia.[27, 22]

An interesting type of arrhythmia sometimes mistaken for acute myocardial infarction[21] is the Wolff-Parkinson-White syndrome (p. 314), in which the electrocardiogram displays a short P-R interval with a bundle branch block pattern. Occasionally acute myocardial infarction is associated with the electrocardiographic changes of the W-P-W syndrome.[116] In such cases the conduction abnormality was usually present prior to the cardiac infarct, but there is a possibility that a septal infarction might impair normal atrioventricular conduction and permit conduction through a previously non-functioning bundle of Kent.[46] Since the electrocardiographic changes of myocardial infarction may be obscured in the presence of a W-P-W pattern,[41a] it has been suggested that the former will become more apparent if a normal conduction mechanism is first restored by the administration of quinidine.[102]

Acute Pericarditis. The combination of chest pain, fever and a pericardial rub may present difficulty in distinguishing between an acute pericarditis and acute myocardial infarction associated with pericardial involvement.[110] A previous history of hypertension and angina pectoris, the presence of gallop rhythm, a fall in blood pressure and other features described above may betray the presence of myocardial infarction, while evidence of some underlying disease such as rheumatic fever, tuberculosis, left-sided pneumonia or pleurisy, or pulmonary or mediastinal neoplasm indicates that the pericarditis is not due to myocardial infarction. The pain of acute pericarditis is often different from that of cardiac infarction in that it may be intensified by cough and deep respiration. The rub is more constant and prolonged. Certain forms of benign idiopathic pericarditis[9, 43] occurring in young persons are often accompanied only by fever, mild pain and a considerable pericardial effusion which is very unusual in cases of cardiac infarction. However, in 6 of 17 such cases reported by Logue and Wendkos,[53] myocardial infarction had been diagnosed or considered. The electrocardiographic distinction has been discussed (p. 468).

Spontaneous Pneumothorax. The sudden severe pain ignited by this condition may inspire a diagnosis of acute cardiac infarction. But the pain is usually sharper and more localized to a side of the chest than to the sternal region as in acute myocardial infarction. The initial spontaneous pain is more transient while subsequent pain occurs or is intensified with deep inspiration or change in posture. Dizziness and dyspnea are common, but the dyspnea is likely to occur only with effort or when turning to the side. Hyperresonance, a diminution or absence of breath sounds over the affected part of the chest and sometimes a shift in the position of the heart may reveal the diagnosis. But often fluoroscopic or roentgenographic examination is necessary. Sometimes the diagnosis of spontaneous pneumothorax is made only when, negative electrocardiographic findings having discredited a tentative diagnosis of cardiac infarction, the chest is examined roentgenologically.

Dissecting (Nonsyphilitic) Aneurysm of the Aorta. This condition, formerly misinterpreted as acute myocardial infarction, is now being diagnosed during life with increasing frequency.[82, 95, 70, 52, 10] Like cardiac infarction, dissecting aortic aneurysm occurs predominantly among males between the ages of forty and seventy with preexisting hypertension. However dissection of the aorta is not as uncommon among young adults as was formerly believed, especially in association with pregnancy and with coarctation of the aorta.[94, 41] In young individuals, in particular, dissecting aneurysm of the aorta may occur in the absence of hypertension, unless there is an associated coarctation.[74]

Weakness of the media due to degenerative disease is the basic disturbance.[23, 49, 93] Rupture of branches of the vasa vasorum causes a tear through the intimal surface and permits subsequent dissection of the main aortic blood stream along the outer layers of the diseased media. The rupture and dissection may be favored by pronounced hypertension, which may have mounted suddenly because of physical effort or emotional strain. But this relationship may only be a coincidence. The intimal tear occurs commonly a few centimeters above the aortic valve or near the origin of the left subclavian artery, but it may occur anywhere in the thoracic aorta and there may be multiple tears. When there is a transverse laceration across the commissures, the latter may slip down and the aortic cusps may not approximate, with consequent aortic

insufficiency.[32] The tear may heal without rupture of the aorta or dissecting aneurysm and the patient may succumb eventually from congestive heart failure due to aortic insufficiency. Or else the blood may dissect its way throughout the thoracic and abdominal aorta involving various large branches such as the coronary, the innominate, carotid, subclavian, intercostal or iliac arteries. One or more of these vessels may be partially or completely occluded by blood clot.

Death usually occurs suddenly, after a relatively quiescent stage of a few hours or days, but sometimes only after months or years. According to Mote and Carr,[74] dissecting aneurysm of the aorta is responsible for 1 per cent of nontraumatic sudden deaths in coroners' statistics. Death is due usually to a perforation of the aneurysm through the adventitia into the pericardium with subsequent hemopericardium and cardiac tamponade.[10] But the aneurysm may also perforate into the left pleural cavity or more rarely into the mediastinum, right pleural cavity or pulmonary artery, or into the abdominal cavity by way of the retroperitoneal tissues. Occasionally recovery is possible when the dissection leads back through a second intimal perforation into the original aortic lumen, producing the so-called double-barreled aorta.[90] But even this healed channel is subject to subsequent rupture.[83]

Although many of the symptoms of dissecting aortic aneurysm resemble those of acute myocardial infarction, a careful history of the onset and development of symptoms, and detailed examination usually permit a distinction.[11] In both conditions there is usually a history of hypertension, but its absence is much rarer with dissecting aneurysm. Of greater diagnostic significance is the persistence of hypertension even when there is evidence of shock after the onset of the dissection. A difference in blood pressure in the two arms favors dissecting aneurysm. In both conditions there is severe retrosternal or precordial pain, but the pain of dissecting aortic aneurysm usually occurs more suddenly, is often of an immediate tearing quality and is apt to have more widespread radiation to the back of the head and neck, the posterior thorax, the lumbar region, the epigastrium or the lower extremities. Dizziness or syncope, nausea and vomiting, dyspnea and cold clammy extremities are common to both, but with dissecting aortic aneurysm, temporary loss of vision, numbness in one or both legs or arms, paralysis of an extremity, or transient changes in reflexes and hematuria are much more common at the outset. Dysphagia due to pressure of the false sac on the esophagus occurs rarely; when present, however, it is a distinguishing diagnostic feature, for it is not encountered with acute myocardial infarction.

The physical signs of dissecting aortic aneurysm are not distinctive, but gallop rhythm and a pericardial rub are absent and the heart sounds are of surprisingly good quality; there may be a systolic murmur over the precordium or an aortic diastolic murmur. There may be signs of a left pleural effusion. Pulsations may be absent in branches of the subclavian or iliac artery. There may be bizarre neurologic changes in the legs due to circulatory deficiency of the cord caused by rupture into the intercostal or lumbar arteries.[104] Due to the absorption of old blood, the icterus index is often elevated, the elevation sometimes persisting for two weeks if the patient survives that long. Pronounced anemia may occur and its presence favors a diagnosis of dissecting aneurysm rather than myocardial infarction.

Roentgenologic examination sometimes discloses a distinctive widening of

the aorta which may appear irregular and distorted by shadows along its branches.[111] Successive films may show distinctive evidence of extension of the dissection. Angiocardiography may reveal constriction of the aortic lumen.[29a]

Absence of the typical electrocardiographic changes of acute cardiac infarction is a critical differential diagnostic feature, but there may be nonspecific RST and T wave alterations. Occasionally, a dissecting aortic aneurysm may produce myocardial infarction by extending along a major coronary artery and thus forming a hematoma, the pressure of which occludes the lumen.

Spontaneous Interstitial Emphysema of the Lung (Mediastinal Emphysema). Hamman[36] called attention to the spontaneous occurrence of mediastinal emphysema without antecedent trauma in apparently healthy individuals and to the possibility of its confusion with acute myocardial infarction. Similar cases have been reviewed by McGuire and Bean[72] up to 1939, and more recent bibliography may be found in the report by Fagin and Schwab.[24] Spontaneous mediastinal emphysema may be characterized by an abrupt onset of severe chest pain in the substernal region, radiating to the neck and left arm; in cases with these symptoms a diagnosis of myocardial infarction appears plausible. Although shock is usually absent, its occurrence in one case increased the resemblance to myocardial infarction.[84] Hamman[36] and others[24] noted inverted T waves in the electrocardiogram. McCabe[65] reported a case of mediastinal emphysema in which there were RST segment deviations in leads I and II. But the true cause of the pain may be betrayed by the pathognomonic sign of very loud peculiar crunching, crackling or bubbling sounds over the sternum and precordium synchronous with cardiac systole and occasionally also with diastole. Sometimes the sounds are heard only when the patient lies on one side or the other. These sounds are probably due to cardiac compression of the air in the mediastinum. Other features distinguishing spontaneous mediastinal emphysema include variations in the pain with change in the patient's position, the frequent association of subcutaneous emphysema, especially in the tissues of the neck and thorax, and occasionally physical or roentgenologic signs of associated pneumothorax. Roentgenograms of the chest may also reveal shadows of air in the mediastinum itself.[73, 1]

According to Macklin,[55] interstitial emphysema of the lung results from increased intraalveolar tension which forces air from the alveoli into the adjacent vascular sheaths, along which the air dissects its way to the mediastinum. It is important not to mistake mediastinal emphysema for acute myocardial infarction, since the former condition runs a benign course with complete recovery in several days. Occasionally, however, it may recur.

Many *other diseases of the thoracic organs or chest wall* may on occasion simulate or be simulated by acute cardiac infarction. These include syphilitic aortitis with aortic aneurysm, pneumonia, pleurisy, massive collapse of the lung, carcinoma of the lung, diaphragmatic or paraesophageal hernia, herpes zoster, costochondral arthritis, rupture of the costochondral junction, and diseases of the spine[16] or shoulder with referred pain to the anterior chest. An awareness of these possibilities and a careful regard for the previous history, development of symptoms and systematic examination including electrocardiography and roentgen examination of the chest will almost always permit a differentiation. In instances of malignant neoplasms of the lung, mediastinum or esophagus, invasion of the pericardium and heart wall may occur resulting not

only in chest pain, but in electrocardiographic changes such as RST elevations, as in the case reported by Rosenbaum et al.[91]

Attention should be called also to malingerers familiar with the symptoms of cardiac infarction, whose complaints are designed to obtain disability insurance payments, injections of opiates if they are addicts, or other benefits. Such dissemblers may even take digitalis to produce electrocardiographic changes, which, however, are usually distinctive of that drug (p. 191).

Cardiac neuroses associated with palpitation or vague precordial pains usually near the apex of the heart or in the supracardiac region are more apt to be confused with angina pectoris than with acute myocardial infarction (p. 383).

Abdominal Conditions Resembling Cardiac Infarction

Acute Indigestion. The error of diagnosing acute cardiac infarction as acute indigestion is becoming less common. With cardiac infarction, there is characteristic retrosternal pain, often with typical radiation, as well as symptoms of indigestion. On the other hand, I have observed a growing tendency to err in the opposite direction by labeling many episodes of indigestion as myocardial infarction. A definite diagnosis of cardiac infarction should be made only if the clinical features, the electrocardiographic changes or both are sufficiently characteristic.

Acute Surgical Abdominal Disease. Radiation or predominance of the pain of myocardial infarction over the upper abdomen accompanied by evidence of shock may compose a clinical picture resembling an acute surgical condition of the abdomen,[48, 108] such as a perforated peptic ulcer, cholelithiasis and acute cholecystitis, acute pancreatitis, acute intestinal obstruction or even acute appendicitis. Conversely, sometimes one of these conditions as well as an attack of renal or ureteral colic with reflex ileus and pain in the abdomen or chest, biliary colic, sigmoid spasm, food poisoning, a tabetic crisis or other abdominal disease[8] may be mistaken for cardiac infarction. Further ambiguity is contributed by the electrocardiographic changes which sometimes accompany a perforated peptic ulcer,[71, 75] acute pancreatitis[31] and acute postoperative peritonitis.[6] However, these changes should rarely be confused with those characteristic of acute myocardial infarction. Careful study of the past and present illnesses will usually result in a proper differentiation.

Among other conditions reported as occasionally simulating cardiac infarction are diabetic coma, sickle-cell anemia during a hemolytic crisis[115] and Addison's disease during a crisis.[92] Although electrocardiographic changes may occur in these conditions, they do not closely approximate the characteristic patterns associated with cardiac infarction (p. 442).

PROGNOSIS

Mortality Rate of the Acute Attack

The outcome of an attack of acute cardiac infarction is unpredictable, on the one hand because of the constant threat of sudden unexpected death, even for persons convalescing favorably, and on the other hand because of the possibility of long survival even for persons apparently critically ill. The mortality rate from the acute attack of myocardial infarction (i.e., within four to six weeks after onset) has been reported by many observers as averaging about 40

to 50 per cent.[15, 112] However, Bland and White[12] reported an immediate mortality (first four weeks) of 19 per cent in 200 cases of coronary thrombosis (many of whom had already survived the critical period when first seen in consultation), and Master, Jaffe and Dack[63] reported a mortality rate of 16.5 per cent in 267 attacks. Among patients apparently suffering their first attack of acute coronary thrombosis these observers noted a mortality rate of only 8 per cent.

It is probable that as milder cases are identified, the mortality rate from first attacks of acute myocardial infarction, excluding those in which death struck before a physician was consulted, will not greatly exceed 10 per cent. Many mild cases treated at home by the family physician are not included in the statistics reported from large hospitals or by cardiac specialists who are apt to see the most severe cases. Autopsy findings indicate that death occurs in a great majority of instances after multiple coronary occlusions; thus, not only is survival the rule after the first occlusion, but this attack is often unrecognizable or unrecognized clinically.

Most deaths from acute myocardial infarction occur within the first week and a large percentage within the first forty-eight hours. With allowance for the possibility of sudden unexpected death at any time, the outlook for survival of the acute attack improves as the first week elapses without complications. The second week remains a critical period, with danger of sudden death from pulmonary embolism, ventricular fibrillation, cardiac standstill or cardiac rupture, or of more gradual death from congestive heart failure, bronchopneumonia, progressive myocardial infarction or peripheral emboli. After the second week recovery from the acute attack is probable if there is no fever, little or no evidence of heart failure and no other gross complications persisting from the earlier stages.

Factors Influencing Prognosis

Age. Most observers have found the mortality to increase with the age of the patient.[88] Woods and Barnes[112] noted that the mortality was twice as great beyond the age of sixty as below. However, I have been impressed by the relatively high percentage of patients who died of their first attack of myocardial infarction below the age of forty. In most of these there was a bad family history of frequent coronary disease. But young persons who recover from the acute attack survive much longer than older recovered patients, and are more apt to be free from evidence of congestive heart failure and angina pectoris.[60]

Previous Attacks of Myocardial Infarction. The mortality rate is significantly higher in patients presenting a history or evidence of previous attacks of acute myocardial infarction.[112, 63] This applies particularly to those patients who suffer from chronic heart failure as a result of the previous attack or whose fresh attack was characterized by the initiation or intensification of congestive heart failure.

Severity and Duration of Pain. The severity of the pain is not in itself of prognostic importance. But it is my impression that when the pain remains intractable, or is only slightly alleviated by opiates after the first twenty-four hours, the outlook for survival is usually unfavorable.

Shock. When myocardial infarction is accompanied by an extreme degree

of shock, or when evidence of shock persists after several days, the outlook is unfavorable. That the mortality has been found relatively high in patients whose blood pressure falls to 80 mm. Hg or less, or whose pulse pressure is 20 mm. or less,[100, 88] merely expresses the same fact since these merely attest to the severity of shock. Occasionally this extravagant drop in blood pressure is followed by a considerable rise after twelve hours and the patient subsequently recovers.

Heart Failure. Since heart failure is one of the chief causes of death during the acute attack, the development of acute pulmonary edema or of other symptoms of left- or right-sided heart failure is inauspicious. Yet it should not be viewed ominously unless it persists beyond the first week, since some evidence of left ventricular failure occurs frequently at the very onset of acute myocardial infarction. In the presence of persistent gallop rhythm the mortality rate is considerably higher than in its absence; but since this sign is an expression of left ventricular failure, it has the same prognostic significance as the latter. Similarly, a heart rate of 110 or higher during the first week of the attack usually is associated with heart failure, with or without shock, and has been found to be an unfavorable prognostic sign.[60]

Fever and Leukocytosis. In general, temperatures of 104 or higher, or a white blood count above 20,000, denotes extensive or progressive myocardial infarction or a serious complication and is associated with a high incidence of mortality.[96] A similar significance is attached to the persistence of even moderate fever and leukocytosis for more than one week after the onset of the attack.

Electrocardiographic Changes. Although it was formerly thought that a typical electrocardiographic pattern of anterior wall infarction augured a somewhat higher mortality rate than that of infarction of the posterior wall, it now appears that the location of the infarct has not in itself prognostic significance.[60, 112] However, when the electrocardiographic changes are not clearly those of either anterior or posterior wall infarction, the mortality rate seems to be higher,[112, 13] perhaps because the indefinite electrocardiographic patterns usually denote multiple cardiac infarcts.

Cardiac Arrhythmias. Among the electrocardiographic alterations which augur a grave prognosis are those which delineate certain cardiac arrhythmias. The mortality rate is probably significantly increased when auricular fibrillation or flutter, ventricular tachycardia, or signs of intraventricular block are present. However, Edeiken[20] recorded recovery from acute myocardial infarction of a patient with a ventricular rate exceeding 300. According to Askey and Neurath,[3] cardiac infarction is associated with a higher mortality when auricular fibrillation is present than in its absence, but the mortality rate is strikingly increased only if the fibrillation persists. A very high mortality rate is associated with the development of complete heart block, especially when symptoms of the Adams-Stokes syndrome appear. Premature beats occurring infrequently are of no significance. But Woods and Barnes[112] noted that among patients with one or more premature ventricular beats in every ten normal beats 14 of 17 died, whereas all of the group with one premature beat in twenty or more survived.

Embolization. The occurrence of pulmonary, cerebral, visceral or peripheral embolism is associated with a high mortality.

Prognosis After Recovery from the Acute Attack

Following recovery from the acute attack, the patient's outlook is much more favorable than was formerly recognized. At least 25 per cent of the patients survive for more than ten years, and at least 50 per cent for five years or longer. Of Bland and White's[12] 162 patients who recovered from the immediate attack, 31 per cent survived for ten years or longer, and 18 per cent were alive at their last follow-up. The younger the patient at the onset, the longer was the period of survival. There are frequent instances of survival for fifteen years, even in the presence of ventricular aneurysm,[85] and occasional ones for twenty-five years or longer.[106] Recently Drake[18] reported a proven case of cardiac infarction in which the patient survived for forty years after the first attack at the age of forty. These statistics are presented not to minimize the seriousness of acute myocardial infarction, but to mitigate in part the excessive pessimism it inspires. The thought of possible long and useful survival is particularly sustaining to patients who associate "heart attack" only with sudden death, limited duration of life and invalidism.

Residual Symptoms and Rehabilitation after Acute Cardiac Infarction

Unfortunately, in a majority of cases recovery from the acute attack is followed by distressing symptoms, restricted activity or invalidism. Palmer[80] found that of 212 patients who had survived three months or longer after coronary thrombosis, about one-fourth were able to lead fairly active lives. Similarly Bland and White,[12] in a study of 162 private patients who survived the acute attack, and Master, Dack and Jaffe,[61] in a study of 202 hospital ward patients, noted that about one third of each group could pursue a fairly active life with little or no restriction because of cardiac symptoms. Bland and White[12] found the longest period of survival in this relatively asymptomatic group, 56 per cent of whom survived for at least ten years, and only 1 of whom developed congestive heart failure. When death eventually occurred in patients of this most favorable group, it was usually caused by another and fatal coronary occlusion or it came suddenly and unexpectedly.

Patients who are able to resume gainful employment after surviving the acute attack of myocardial infarction represent a larger percentage than the asymptomatic group because many who continue to suffer anginal pain or mild dyspnea are nevertheless able to work. Fifty-three per cent of 415 private and hospital ward patients followed by Master and Dack[50] and 74 per cent of 84 patients studied by Levine and Phillips[47] returned to work following recovery from their acute attack. In 32 per cent of the former group the work was full time and in 21 per cent, part time. Complete economic restitution, i. e., return to full time work, was almost twice as frequent among the private as among the ward patients. The younger the patient, the more probable was his return to work. Slightly more than 90 per cent of those who resumed their work did so within one year, about 75 per cent within six months and slightly more than 50 per cent within three months after getting out of bed or leaving the hospital.

The largest group of recovered patients were those whose activities were restricted in varying degree because of disability from residual symptoms, chief of which were angina pectoris, dyspnea on effort or at rest, and weakness or easy fatigability. These symptoms individually or in combination were present in two thirds of the patients followed by Bland and White[12] and Master et al.[61]

Angina Pectoris. Occasionally patients who have suffered from angina pectoris lose their pain after an attack of acute myocardial infarction, probably because the anoxic muscle responsible for the pain is no longer viable. Much more often attacks of angina pectoris on effort or at rest persist after cardiac infarction and in about half of the cases in which angina pectoris is absent before the attack, it develops after recovery from the acute infarct. Palmer[80] and Master et al.[61] observed angina pectoris in about 60 per cent of the patients who had recovered from an acute cardiac infarct, a higher incidence than before the attack. Furthermore the attacks of angina pectoris usually occurred more often, and were more persistent and more readily induced by minor exertion or at rest than previously. Bland and White[12] found that one third of their patients who recovered from the acute attack were limited in their activity by angina pectoris alone. In this group only one third survived for ten years or longer as compared to 56 per cent in the recovered group without symptoms.

Hypertension is more apt to disappear after cardiac infarction than is angina pectoris. The blood pressure remains at relatively normal levels in one third to one half of the cases in which hypertension existed before the attack.[64] In the remainder the blood pressure gradually rises to a hypertensive level which is somewhat below that prior to the attack.[79] According to Chambers[14] 58 per cent regain hypertension within two years. Occasionally the blood pressure eventually exceeds that before the cardiac infarction. In patients with normal blood pressure before cardiac infarction, the blood pressure may gradually return to the previous level, but often it is 10 to 20 mm. lower and may even remain at hypotensive levels (below 100 mm.).

Neither the degree of hypertension if present nor the absence of hypertension after cardiac infarction appears to be related to the appearance, disappearance or persistence of angina pectoris after the attack. Observations as to the influence of hypertension on the subsequent course of the disease including the development of heart failure and the duration of life are in disagreement, but in my experience heart failure occurs more frequently and the outlook for life tends to be less favorable in those in whom hypertension recurs.

Heart Failure. Dyspnea was a consistent complaint in more than half of the patients followed in the study by Master, Dack and Jaffe,[62] while objective evidences of heart failure, usually of the left ventricle, were observed in about one quarter of their patients. Dyspnea restricted the activity of about one third of the patients followed by Bland and White[12] who had survived an acute attack of coronary occlusion. This group pursued a much less favorable course than either those who were free from symptoms, or even those who suffered from angina pectoris after their recovery from the acute attack. None of them survived a ten year period, and 75 per cent of the patients with dyspnea succumbed because of congestive heart failure. It is interesting that symptoms or signs of left heart failure which appear in half to two thirds of the patients during the acute attack disappear in a majority of those who recover. Occasionally, dyspnea and angina pectoris are present in the same patient.

Cardiac enlargement following recovery from myocardial infarction is observed in more than half the cases. When it is of considerable degree, it is associated with persistent manifestations of congestive heart failure. Consequently, restriction of activity occurs much more regularly when cardiac enlargement follows myocardial infarction.[80] Conversely, a normal cardiac size

following recovery from the acute attack usually promises a better clinical recovery and a favorable outlook for normal activity.

Electrocardiographic Changes Following Recovery. The electrocardiogram returns to normal in about 20 per cent of cases, usually within a year after the attack. The majority of these patients, as well as patients in whom the T waves become normal while the Q waves persist, make a favorable recovery.[61] In the remainder, Q waves, inverted T waves or T waves of low voltage, or slurred, notched and prolonged QRS complexes persist without necessarily denoting an unfavorable prognosis.

Subsequent Attacks of Cardiac Infarction

Regardless of the outcome after an acute cardiac infarction, the further outlook for the patient is clouded by the danger of further episodes of coronary occlusion and cardiac infarction. Clinical studies indicate that such additional attacks recur in about 30 per cent of cases, usually within two years after the first attack. However, pathologic studies attest to a much higher incidence of recurrent coronary occlusion. These new episodes are often overlooked because the clinical features either are not as characteristic as those of the first attack or are overshadowed by symptoms and signs of congestive heart failure, and because the electrocardiographic changes when superimposed on previous abnormalities are often not specific. Each additional attack of cardiac infarction either increases the probability of a fatality, or leaves the patient more subject to the development or intensification of congestive heart failure or disabling attacks of angina pectoris than after the first infarct.

Effect of Patient's Cooperation and Morale

In concluding this discussion of factors modifying the prognosis after cardiac infarction, it is well to emphasize the importance of certain less easily measured influences. These include the cooperation of the patient with his physician in making the necessary modifications in his diet, in his hours of sleep and rest, and in the character and duration of his work or other activities without resentment or moroseness at his unfortunate fate. The success with which these adjustments are accomplished is dependent in general on the patient's capacity for a healthy optimism and contented readjustment despite essential restriction, and also in large measure on the wise and tactful management of an understanding, reasonable and practical physician.

TREATMENT OF ACUTE CARDIAC INFARCTION

Treatment of the Acute Attack—General Survey

The treatment of acute cardiac infarction is designed: (1) to reduce the work of the heart until the infarcted area is healed, (2) to alleviate pain or other discomfort, (3) to overcome shock and cardiac failure if present, and (4) to cope with dangerous cardiac arrhythmias or any complications that may arise.

Rest in bed is the mainstay of treatment. It should be instituted promptly whether the symptoms are mild or severe and even if there are no longer any subjective complaints when the patient is first seen. If the attack occurs away from home, the patient should be transported to the hospital or to his home by ambulance. (For a detailed discussion of this and related measures, see below,

p. 483). In addition to putting the patient to bed in order to diminish the work of the injured heart muscle, some physicians administer atropine hypodermically or intravenously (p. 490), papaverine intramuscularly or intravenously (p. 491), or aminophylline intravenously (p. 491). The first is intended to prevent reflex vagal vasoconstriction of the coronary arteries, and the latter two are given to produce coronary vasodilatation. Whether these drugs accomplish the purpose for which they are intended is questionable.

Other measures are instituted according to the urgency and predominance of individual symptoms.

Symptomatic Treatment

Pain. As a rule, *morphine or other opiates* (p. 488) are administered to control severe *pain, restlessness and anxiety* at the onset of the attack, but morphine is not essential if the pain is relatively mild and can be relieved by codeine or weaker analgesics. If the pain has already subsided, none of these drugs need be used, but mild sedatives may be advisable (p. 492). If extremely severe pain is unrelieved by opiates, it may sometimes be controlled by oxygen therapy (p. 487), and by the intravenous administration of aminophylline (p. 491).

Shock. Shock may be an urgent and dominating feature of cardiac infarction, but there is no satisfactory, specific treatment. Therapeutic measures ordinarily employed in other forms of shock may be dangerous, lest they overload the circulation, or strain the injured heart muscle. Of course rest in bed, and the alleviation of pain, restlessness and anxiety by opiates are indirectly helpful. But in the absence of pain and restlessness opiates should be withheld, as they tend to depress pulmonary and tissue respiration and intensify the anoxia already present.

The *intravenous administration* of 50 to 100 cc. of *50 per cent glucose,* repeated after eight to twelve hours if necessary, offers the theoretical advantages of increasing the circulating blood volume and of providing nourishment for myocardial metabolism. Ginsberg et al.[29] have reported a significant and sustained increase in the coronary flow of intact dogs following the intravenous administration of 50 per cent glucose. But I have not observed any distinct clinical improvement from its use in patients with acute myocardial infarction. *Small transfusions* of 150 to 250 cc. of blood or plasma are sometimes given very slowly but there is always a danger of inducing pulmonary edema. If pulmonary edema is already combined with evidences of shock, transfusions are entirely contraindicated. The same objections apply even more emphatically to the administration of larger quantities of isotonic saline. Bandaging of the lower extremities has also been advised to alleviate shock by increasing the circulating blood volume. However, it is doubtful whether these measures to increase circulating blood volume influence the shock which is due to direct cardiac injury.

The application of external heat to the extremities, other than a supply of blankets adequate to preserve body warmth, is now considered of dubious value if not detrimental in the treatment of shock. Furthermore, external heat may intensify perspiration in patients who are already dehydrated from loss of fluids. There is the additional danger that external heat may readily cause burns in skin in which the blood vessels are constricted.

In critical instances of cardiac shock with an immediate danger of death,

small doses of *epinephrine* (3 to 5 minims of 1:1000 solution) may be injected subcutaneously or intramuscularly, or epinephrine (1 cc. of 1:1000 solution) in a liter of 5 per cent glucose may be injected intravenously by very slow drip (0.5 to 1.0 cc. per minute) until the most acute stage of shock is overcome. Or else, after the first parenteral injection of epinephrine, *ephedrine sulfate* may be given subcutaneously in doses of 0.015 to 0.03 gm. (¼ to ½ grain) for more prolonged action. Because of the possible danger of increasing the work of the heart without a concomitant augmentation of the coronary blood flow, these drugs should be used only rarely and with caution. *Paredrine* and *neo-synephrine* are other sympathomimetic amine drugs which may be used in critical instances of shock. They have the advantage of raising blood pressure without accelerating the heart rate or causing significant central stimulation as does epinephrine or ephedrine. Their effect is much more prolonged. Paredrine may be given intramuscularly in doses of 5 to 10 mg. and neo-synephrine subcutaneously or intramuscularly in doses of 3 to 5 mg.

Acute Left Ventricular Failure. In the presence of acute left ventricular failure characterized by pulmonary edema, immediate and sometimes drastic therapeutic measures must be instituted (p. 207). Morphine or other opiates should be administered subcutaneously, as indicated in order to control intense dyspnea as well as anxiety or pain. If morphine is ineffective, the *slow intravenous injection of 0.5 gm. of aminophylline* in 20 cc. solution may occasionally control pulmonary edema by relaxing the bronchial musculature.

While the question of using *digitalis or strophanthin* in acute left ventricular failure due to cardiac infarction is moot (see below, p. 493), dramatic relief of acute pulmonary edema sometimes follows the intravenous injection of 0.25 mg. (1/240 grain) of ouabain (p. 187), repeated if necessary in one-half hour to one hour, in patients who have not received digitalis in the previous two weeks.

Oxygen should be administered in high concentration (80 per cent or more), or preferably under positive pressure.[7] Usually this measure is effective in controlling the anoxemia and cyanosis associated with severe pulmonary edema. But positive pressure should not be used if pulmonary edema is accompanied by shock.

Tourniquets and venesection, often enlisted in the treatment of other forms of pulmonary edema, *should not be employed routinely* when this condition is due to cardiac infarction. For in these cases the pulmonary edema is often associated with severe shock and the venous pressure is low, the peripheral veins collapsed and the venous return diminished by reflex vasoconstriction of the arterioles. There is thus no need for external venous compression by tourniquets, and venesection may further diminish dangerously the circulating blood volume and the cardiac output.

However, in the absence of shock and especially when acute pulmonary edema is associated with right-sided heart failure and systemic venous engorgement, the application of tourniquets to all four extremities, with sufficient pressure to occlude the veins but not the arteries, may help control pulmonary edema by diminishing the venous return to the right side of the heart and lungs. Kountz et al.[42] have described an instrument for rhythmic inflation and deflation in rotation of cuffs placed on the arms and thighs, to which they have attributed great therapeutic value in the management of acute left ventricular failure and myocardial infarction. In extreme cases of pulmonary

edema with increased systemic venous pressure, the removal of 350 to 500 cc. of blood may be lifesaving, but this should not be performed if there is anemia.

When acute left ventricular failure is characterized only by moderately severe dyspnea and orthopnea, without pulmonary edema, the subjective discomfort may be controlled by morphine or other opiates, oxygen therapy and rest in bed with elevation of the patient's head and shoulders by pillows. Nocturnal dyspnea or Cheyne-Stokes respiration may be alleviated by the intravenous administration of aminophylline. If nocturnal dyspnea or orthopnea is severe and intractable, it may be relieved by the intravenous administration of ouabain, followed by a mercurial diuretic (p. 194). In addition a sharp restriction of the intake of sodium and limitation of fluids are necessary.

Individual Therapeutic Measures and Drugs

Bed Rest. It is generally considered that patients suffering from an acute myocardial infarction should be put to bed for an average period of six weeks. Rest is a traditional principle of treatment of a diseased organ, and as applied to the heart is intended to diminish its work. This recommended rest period is based on relatively limited pathologic studies which indicate that six weeks are required for the infarct to be converted into a firm scar,[56] and experimental studies showing that at least three weeks are necessary for the development of a collateral circulation to supplement the interrupted blood supply.[19] It seems unreasonable, however, that the same fixed period of bed rest should be prescribed for all patients with acute myocardial infarction, whether they are critically ill or asymptomatic after a brief episode of pain, whether there be relatively high and prolonged fever or slight fever for only a few days, and whether or not they suffer from shock, pulmonary edema, congestive heart failure or serious complications.

Most of the fatalities and complications from acute myocardial infarction occur during the first week, a more moderate number in the second week and relatively few in the third week. For this reason, it is my policy to insist on a minimum of two to three weeks of rest in bed. But, as discussed below, this does not mean complete immobility or even complete restriction to bed for every minute of that period. For an additional period of three to four weeks (making an average total of six weeks), the patient is confined to bed most of the time. But within the confines of his bedroom or his hospital room, he is permitted moderate liberties which do not involve more than the simplest exertions and do not result in mental or emotional strain. Serial observations of the sedimentation rate in addition to clinical observation assist in determining the proper duration of confinement. As a rule, increased liberties are permitted only when the sedimentation rate has returned to normal.

This average period of six weeks is designed to permit recovery from the acute attack and permit healing of the infarct. It does not include a further period of weeks or months of convalescence to permit the gradual resumption of a permanent routine. Furthermore, this average period does not allow for the occurrence of complications, the development of chronic left- or right-sided heart failure, frequent attacks of angina pectoris, or extreme weakness, which may extensively prolong the period of rest in bed or of greatly limited activity.

The rigid severity with which bed rest is usually enforced has recently led to considerable public expression of the dangers of the injudicious and exaggerated application of this therapeutic measure (p. 162). It has long seemed

reasonable to assume that "complete rest" is desirable for the acutely infarcted heart muscle until healing ensues. Physical exertions have been feared because of the risk of rupture of the softened myocardium. Myocardial infarcts produced experimentally in dogs were found to heal with a small strong scar when the dogs were rested for six days after infarction, while aneurysmal bulging and a thin scar resulted if the dogs were exercised in the first three days after infarction.[101] On the other hand, it may be questioned whether most patients would be harmed by such simple activities as feeding themselves or using a commode instead of a bedpan. Moreover the advantages of bed rest must be weighed in individual cases against the deterioration of morale, the frequency of constipation and abdominal distention, the circulatory strain often involved in the use of the bedpan, the occurrence of disabling muscular and ligamentous strains, especially of the back or the shoulders, the development of bedsores, the risk of decalcification of the bones, especially in the elderly, and the occurrence of urinary disability if not retention in patients with moderate prostatic hypertrophy.

If patients with orthopnea, cardiac asthma or pulmonary edema are forbidden to sit in a chair or upright in bed, disability is increased. The disadvantages of recumbency to such patients have been mentioned (p. 162). The dangers of hypostatic congestion and bronchopneumonia increase with the degree of immobility of the patient. But most important of all, pulmonary embolism, one of the very common causes of death from myocardial infarction, may be attributed primarily to venous stasis and thrombosis of the leg veins caused by strict and prolonged bed rest. Pulmonary embolism is sometimes precipitated by extreme straining at stool and this danger is enhanced in many patients who are forced to use the bedpan even when this necessitates excessive straining.

These considerations should lead to careful reflection before ordering complete bed rest for a fixed period of time as soon as the diagnosis of acute myocardial infarction has been made. It has long been my custom to permit patients to feed themselves, to move freely in bed and to perform leg exercises (especially dorsiflexion of the feet with contraction of the calf muscles) at regular frequent intervals as soon as possible after the onset of the attack. If the patient is capable of using the commode and has found real difficulty in using a bedpan, I have permitted the former. Above all, management should be sufficiently elastic to permit desirable modification in individual cases. The recent tendency to liberalize the meaning of bed rest in cases of myocardial infarction will prove to be beneficial only if it does not lead to the opposite extreme of utterly neglecting this fundamental therapeutic measure.

Rest in bed for the patient recovering from acute myocardial infarction means not only avoidance of physical exercise but complete mental repose and protection from emotional strain. These aims cannot always be fully realized, but as far as possible they should be attained by isolation of the patient from outside communications and contacts which produce mental strain or upset him emotionally, by confident reassurance that he will get well, by efficient examination and care of the patient on the part of the doctor and nurse with as infrequent disturbance as possible, and by sufficient medication to keep him free from pain or other discomfort, and to provide adequate sleep.

Hospital versus Home Care. Most patients with acute myocardial infarction can be treated satisfactorily at home. Hospitalization may be preferable when

certain measures such as oxygen therapy are essential and cannot be properly carried out at home, when the patient's home is at a considerable distance from his physician and the severity of the attack and its complications warrant frequent and prompt medical attention, when satisfactory dietary or nursing care cannot be obtained at home, when the patient's activities, or intrusions by relatives, friends or business associates, can only be controlled in the hospital, or when other environmental conditions at home are undesirable. The patient's progress as determined by frequent observation and by electrocardiographic or other laboratory tests can usually be followed more easily and complications treated more promptly at a hospital. If for any of these reasons hospitalization appears preferable, the physician should not be deterred by the exaggerated fear of moving the patient, provided this can be done by ambulance with the aid of trained attendants. An opiate should be administered before transporting him, and other available emergency measures instituted if necessary.

Sometimes hospitalization appears preferable to home treatment for the first two or three weeks, after which treatment may be continued at home. Under these circumstances also, there is no objection to moving the patient if he is recovering satisfactorily and if no excessive exertion on his part is required in the transfer, which should be by ambulance.

Nursing Care. Good nursing care can be a valuable adjunct to treatment. Its purpose should be to help the patient avoid undesirable exertions, to protect him from the telephone and from visits by his business associates, friends and relatives, and to provide a cheerful atmosphere, as well as to administer medications and other therapeutic measures. As indicated above, "too good" nursing may be fraught with danger, if it involves complete restriction of the patient to the point where he lies in bed like an inanimate log.

Diet. In the first week, the diet must be varied according to the patient's condition. When severely ill, he may take only small amounts of fluid at a time, such as fruit juices, milk, broth, tea, ginger ale or water. Care should be taken to avoid distressing abdominal distention in persons intolerant to milk or excessive amounts of fruit juice. Some patients who tolerate milk may be given the Karell diet (200 cc. of milk every four hours) for twenty-four hours or longer. Sodium intake should be restricted if there is evidence of congestive heart failure.

If there is persistent vomiting during the first day or two, 50 cc. of 50 per cent glucose can be given intravenously at regular intervals to provide fluids and carbohydrate. If there is evidence of dehydration due to excessive perspiration and vomiting, small infusions of 5 per cent glucose in saline may be given intravenously very slowly (15 drops per minute or 45 cc. per hour) or by subcutaneous clysis. Similar infusions may be given rectally through a Harris or Murphy drip. These are discontinued as soon as fluids can be taken orally.

As soon as they are tolerated, soft foods are given in addition to fluids. Cooked cereal, soft boiled egg, milk toast, stewed fruit, junket, mashed or baked potato and simple puddings may be given at brief intervals, if necessary, but only in small amounts at any one time.

When the very acute symptoms have subsided (or in mild cases from the very onset), I allow between 1000 and 1200 calories daily, and increase this gradually as the patient is permitted to get out of bed and resume moderate activity. Master and his associates[63] have urged a low caloric diet (800 calories

daily) to reduce the basal metabolic rate and thereby diminish the work of the heart and promote better healing of the infarct. Without questioning the theoretical value of a low caloric intake during the acute phase of myocardial infarction, I doubt the importance which these observers have attached to this single therapeutic measure as a means of lowering mortality. Most patients who succumb do so during the first week when they are too sick to take even this low caloric allowance.

Because of the low fat content and inadequate amounts of the B complex, a suitable multivitamin capsule is given to supplement the diet.

The diet should eliminate foods which are usually difficult to digest, which are likely to cause distention or to which the patient has a sensitivity or special aversion. Raw fruits, fruit juices in excess, fried foods and gravies, spices and condiments, onions, corn, members of the cabbage family, pastries, chocolates, corned or smoked meats and fish, fatty meats and fish, cheeses, nuts, dates, figs and raisins should be avoided. The intake of salt should be minimized in the presence of congestive heart failure.

When the patient resumes moderate activity, his caloric intake should be such as to maintain his weight if it is normal, or to reduce it if he is overweight. Whenever feasible the daily caloric allowance should be divided into five meals to avoid an excessive quantity at any one time.

In the presence of diabetes mellitus, the caloric allowance should be apportioned properly among carbohydrates, proteins and fats. Insulin is discussed below.

Tobacco, Alcohol, Coffee. *Coffee* in moderation is allowed if it does not increase restlessness or cause sleeplessness. *Alcohol* is usually permissible if the patient desires it or is accustomed to it. It has long had the reputation of clinical benefit in angina pectoris, and often appears to benefit the patient during convalescence from an acute myocardial infarction. However, I do not prescribe it for patients who do not take alcoholic drinks ordinarily or who dislike it. To patients who complain of weakness or depression, and especially to elderly patients, I often suggest a trial of alcohol in doses of 15 to 30 cc. (½ to 1 oz.) repeated twice daily; its continuation is dependent on the patient's subjective reaction. The alcohol is given in the form of whiskey, brandy, sherry or other wine. Wine, sherry and beer often act as satisfactory soporifics. Alcoholic beverages should not usually be prescribed if there is prostatism, and they often are detrimental to other possible associated conditions such as definite sinusitis, peptic ulcer and gout.

Despite uncertainty as to the effect of tobacco in cases of myocardial infarction, I usually prohibit its use during the acute phase of the disease. Thereafter it is usually possible to maintain this prohibition; if not I sharply curtail the amount of smoking. There is a distinct clinical impression that tobacco in susceptible individuals precipitates or increases the frequency of anginal pain.

Care of Bowels. After a severe attack it is undesirable that the patient be disturbed or urged to move his bowels for the first three days, as straining at stool may be a dangerous exertion. Usually the patient is constipated during this period because of the low intake of food and especially because of the administration of opiates. Soft easy bowel movements may be effected thereafter with the aid of mineral oil (½ to 1 oz. on retiring) and, if necessary, small doses of milk of magnesia (½ to 1½ oz.) each night. If there is disten-

tion, a small saline enema may be given, preferably after mineral oil with or without a small dose of milk of magnesia has been administered on the previous night. A rectal tube may also be used to help control distention. In extreme cases it may be necessary to give prostigmine, 1 cc. of 1:4000 or 1:2000 solution, intramuscularly.

Whenever obstipation, abdominal distress and distention are associated, the possibility of a fecal impaction induced by opiates should be considered and a rectal examination made. If present, the impaction should be relieved manually. The development of pronounced distention should also suggest the possibility of a pneumonia and the lungs should be carefully examined for this complication. If pneumonia is found to be present, its successful treatment with sulfonamides or penicillin will control the distention more readily than any local abdominal or gastrointestinal measure.

Oxygen Therapy (see also p. 204). The administration of oxygen has become an important therapeutic measure in the management of acute cardiac infarction. However, its usefulness is probably limited to relatively severe cases. Levy and Barach[50] have reported striking relief of pain and restlessness, slower and less labored respiration, diminution or abolition of cyanosis, disappearance of Cheyne-Stokes respiration and other objective signs of improvement within one to three hours after beginning the administration of oxygen. Unfortunately for its evaluation all of the dramatically favorable results observed in individual cases following oxygen therapy can be matched by a similar sequence of events in other cases without the aid of oxygen.

Cyanosis is the clearest clinical indication for oxygen therapy, but mild degrees of cyanosis are easily overlooked clinically, and in the presence of shock cyanosis may be manifested as a grayish or ashen hue. Oxygen therapy is often useful for acute pulmonary edema, especially when supplied by the positive pressure technic.[7] It is often administered in the presence of shock to overcome general tissue as well as myocardial anoxia. Persistent dyspnea is a more definite indication for oxygen therapy, but has not always been effectively controlled by it. Dramatic relief from intractable pain has been reported by some observers. I have yet to note such an impressive and fortunate occurrence although I have occasionally witnessed the partial amelioration of severe pain and the relief of mild pain by oxygen therapy. It should be emphasized that coronary occlusion results primarily in anoxia confined to the affected myocardial tissue, which cannot usually be significantly altered by the administration of oxygen. Oxygen therapy is useful in those cases in which cardiac damage and disturbance in function result in a secondary generalized arterial anoxemia.

In practice it has been my custom to give oxygen therapy a trial in all cases in which there is severe or persistent pain, dyspnea, cardiac asthma, pulmonary edema, Cheyne-Stokes respiration and, of course, cyanosis. This therapy is continued if there is any evidence of objective or subjective improvement of the symptom for which it was administered. As the patient improves and the oxygen is discontinued, it is promptly resumed if there is evidence that the patient was more comfortable during its administration or if objective signs reappear which had been abolished by the oxygen.

When the indication for oxygen therapy is clear-cut, I prefer to use an oxygen tent supplying a concentration of 50 to 60 per cent of oxygen, when the latter runs in at the rate of 9 to 10 liters per minute. The temperature in the tent,

which together with the humidity should be carefully regulated to the patient's comfort, is usually maintained between 60° and 68° F. If a tent is not available or if the patient is not easily managed in the tent, oxygen can usually be administered satisfactorily by means of (1) a BLB mask (provided for auronasal or nasal breathing with a regulator which can deliver up to 100 per cent oxygen), (2) small transparent plasticele face tents which, with a flow of 8 liters per minute, can deliver a concentration of 40 to 60 per cent, or (3) a bilateral nasal or a unilateral auronasal catheter. The latter will provide about 35 per cent oxygen if the flow from the tank is 5 liters per minute, but it is not usually tolerated by the patient.

Drug Therapy. *Morphine and Other Opiates.* Morphine or one of its substitutes is the drug of choice in cases dominated by pain and restlessness, paroxysmal or constant dyspnea or pulmonary edema. The usual dose is 15 mg. (¼ grain) hypodermically, but it may be given intramuscularly when more rapid action is desired. Often this dose must be repeated in one-half to one hour if the symptoms are not alleviated; as much as 60 mg. (1 grain) over a period of four hours may be required in extreme cases. But not more than this total should be given within twelve hours. In extreme cases a prompt effect may be obtained by giving 15 mg. of morphine diluted in 5 to 10 cc. of sterile water into a vein, but respirations should be observed carefully and the injection stopped if the desired result is obtained before the full dose has been administered. Coramine or metrazol should be available and given parenterally if the respiratory rate falls below 12, or they may be given with the morphine.

Because of the respiratory depression which morphine causes, large doses must be given with caution and the patient observed carefully. Standing orders for morphine, with the decision as to its further use left to a nurse, should not be countenanced. It should also be emphasized that morphine should not be given routinely as soon as the diagnosis of myocardial infarction has been made. Mild pain can often be controlled by demerol or codeine, and in some cases even these analgesics are unnecessary. Even if morphine appears desirable, 10 mg. doses (⅙ grain) often suffice after the initial larger dose. Aside from its tendency to depress or paralyze the respiratory center, morphine has other disadvantages due to its constriction of smooth muscle and vagal stimulation. The former results in pronounced constipation which may be extremely distressing and, in predisposed persons, in urinary retention due to spasm of the sphincter of the bladder. The vagal stimulation poses at least the theoretical danger of causing coronary vasoconstriction and of rendering the heart muscle susceptible to ectopic ventricular rhythms.

When large or repeated doses of morphine are used, coramine, metrazol or caffeine may be given at the same time to counteract its respiratory depression, or these drugs may be given later if the respiratory rate falls to 12 per minute or less. *Coramine (nikethamide)* is a respiratory stimulant which reflexly excites the chemoreceptors of the carotid bodies; its effect is greatest when the respiratory center is already depressed by opiates. The dose is 1 to 3 cc. of a 25 per cent solution given intravenously. *Metrazol* (cardiazol) is a camphor related drug with a similar action and probably more effective. The dose is 100 to 300 mg. (in ampules of 1 cc. or 3 cc. of a 10 per cent solution) given parenterally. *Caffeine sodiobenzoate* injected intramuscularly in doses of 0.5 gm. (7½ grains) may also be used for the same purpose. *Aminophylline*

is the drug of choice when respiratory depression is associated with Cheyne-Stokes respiration (p. 201).

Other Opiates and Analgesics. In my experience, most patients vomit after receiving morphine and I have usually substituted *dilaudid,* which causes vomiting much less frequently. Dilaudid is a synthetic drug related to morphine with proportionally more analgesic and less soporific and respiratory depressant effect. Its therapeutic dose is about ⅕ that of morphine. Usually 3 mg. (1/20 grain) is approximately equivalent to 15 mg. (¼ grain) of morphine. *Metopon* is a new synthetic morphine substitute which is a methyl derivative of dilaudid. Its advantages over morphine are said to include much less soporific respiratory depression, greater analgesia, less tendency to produce vomiting or to lead to addiction. The average dose is 6 mg. orally. *Pantopon,* which is a mixture of opium alkaloids, containing chiefly morphine, is said to cause vomiting infrequently, but in my experience it induces vomiting as often as does morphine. The dose of 20 mg. (⅓ grain) of pantopon is about equal to 15 mg. (¼ grain) of morphine. It is probable that its effectiveness is due entirely or almost entirely to the morphine it contains and for this reason it is associated with the same disadvantages and toxicity.[87]

Demerol is a synthetic analgesic, chemically related to morphine and atropine, which is much less apt to cause addiction than morphine. It may be substituted for the latter after the early severe pain subsides and more moderate pain persists or recurs frequently after the first day. Unlike the above opiates it does not result in respiratory or profound cerebral depression. It is administered orally, hypodermically or intramuscularly in doses of 100 mg. and may be repeated if necessary at four to six hour intervals. Its effect is usually observed within twenty minutes after intramuscular injection and thirty minutes after oral administration. In the above dosage it is more effective than 1 grain of codeine.

Codeine in doses of 0.03 to 0.06 gm. (½ to 1 grain) hypodermically or orally may also be substituted for morphine when the severe pain lessens or if the pain is moderate from the beginning.

Anticoagulants—Heparin and Dicumarol. Anticoagulants have been administered to patients with acute myocardial infarction in order to limit the development of complete thrombotic occlusion, or prevent its extension, but especially to avoid the frequent thromboembolic complications, including ventricular mural thrombi, phlebothrombosis of the lower extremities and pulmonary and systemic emboli (p. 882). Early reports have given impressively encouraging results but the number of cases is still too few to permit definite conclusions as to the effectiveness of these drugs. There is sufficient evidence, however, to recommend their routine trial whenever adequate and competent facilities are available for continued determination of coagulation and prothrombin times. Clinical embolism as well as mortality rates have been strikingly reduced in all of the small series of cases treated with anticoagulants as compared with similar series of patients who did not receive these drugs.[86, 113, 81, 25, 66, 30, 33] Statistical analysis[114] of the first 800 cases studied by the Committee for the Evaluation of Coagulants in the Treatment of Coronary Thrombosis showed a mortality rate of about 15 per cent for the group treated with anticoagulants as compared to a mortality rate of 24 per cent for an essentially similar control group and an incidence of 11 per cent of thromboembolic complications in the treated as compared with 25 per cent in the untreated group.

Minor or moderate hemorrhagic manifestations occurred in 12 per cent of the cases treated with anticoagulants as compared to 6 per cent of those without such treatment.

The action, dosage and toxic effects of heparin and Dicumarol are discussed (p. 883) in connection with the treatment of phlebothrombosis and pulmonary embolism (p. 882). Heparin may be given the first two days until the Dicumarol becomes effective or Dicumarol may be administered alone. After the initial prothrombin time is found to be satisfactory, 300 mg. Dicumarol is given by mouth. Daily prothrombin times are determined. Dosage of Dicumarol is adjusted to maintain a prothrombin index (control prothrombin time divided by patient's prothrombin time) of 35 to 50 per cent or a prothrombin time representing 10 to 30 per cent of normal prothrombin concentration (p. 883) for about four weeks. After the first day, Dicumarol is given in doses of 100 to 200 mg. on each day that the prothrombin time is not sufficiently prolonged. (For details, see p. 883.)

Atropine. The value of atropine in the treatment of acute myocardial infarction is unproven and not widely accepted. Its use has been recommended on the basis of experiments on dogs which indicated that after the production of myocardial infarction there is a reflex vasoconstriction of the unaffected coronary arteries, including those which might serve for collateral circulation.[57] These reflexes were believed to be mediated through the vagus nerve because following atropinization the mortality from experimental coronary occlusion was significantly diminished.[44, 68] Both the conclusions drawn from these experiments and their applicability to human myocardial infarction may be questioned.

On the basis of the above experimental observations, Gilbert[28] recommends the prompt administration of 0.6 to 0.8 mg. (1/100 to 1/75 grain) of atropine sulfate hypodermically (not intravenously) in the treatment of acute myocardial infarction. Thereafter it may be repeated in four, six or eight hours until conditions appear stabilized. Usually one to three doses are given. The atropine may be given with the morphine not only to prevent local vagovagal reflexes from the infarcted myocardium as mentioned above, but also to counteract a theoretical vagal stimulation by morphine (p. 488). Atropine has also been recommended when pulmonary embolism complicates myocardial infarction, in order to prevent pulmonary-coronary vagal vasoconstrictor effects. The clinical course of acute myocardial infarction as well as that of pulmonary embolism are too variable to permit an accurate evaluation of atropine in these conditions. In my limited experience with it, I have not been convinced of the usefulness of atropine in myocardial infarction, much less its touted lifesaving qualities. But I can see no serious objection to its being tried (except in the presence of unusual tachycardia) until its effectiveness or uselessness is proven.

Xanthine Drugs. Drugs of the xanthine or purine series, theobromine, theophylline or their derivatives, have been recommended in the treatment of acute myocardial infarction because they are vasodilators. Theophylline and theobromine are usually mixed with ethylenediamine, sodium acetate or sodium salicylate to make them water soluble. It was observed that following experimental ligation of a coronary artery in dogs, the resulting infarcts were smaller after the administration of aminophylline or theobromine sodium acetate than were infarcts produced without the preliminary use of these drugs.[26, 44] But

these observations have not been confirmed by others.[107] As with atropine, I have been unable to convince myself of any distinct value of the xanthine drugs in reducing the mortality from acute myocardial infarction or in producing a striking clinical improvement. However, since occasionally aminophylline has seemed to diminish the cardiac pain, it may be tried for this purpose if other medications have been ineffective. In addition, it undoubtedly often controls cardiac asthma and Cheyne-Stokes breathing. Usually these disturbances recur unless the basic condition due to infarction improves. The xanthines are also useful as diuretics when cardiac infarction is complicated by congestive heart failure.

Aminophylline (theophylline with ethylenediamine) has seemed to be definitely effective only when given intravenously, but I have noted less clear-cut results also with its intramuscular and rectal administration. For other than diuretic purposes, I have been unconvinced of its usefulness in cases of myocardial infarction when given by the oral route. The intravenous dose of aminophylline is 0.25 gm. (3¾ grains), which is available in a 10 cc. ampule, or 0.5 gm. (7½ grains) in a 20 cc. ampule. These are repeated two or three times daily during the most acute phase of the infarction. *Slow administration,* through a fine needle (22 gauge), is extremely important because of the danger of rapid vasodilatation and a drop in blood pressure, which may prove fatal. Palpitation, headache, nausea, chest pain and syncope are other symptoms caused by too rapid injection.

Aminophylline for intramuscular use is available in 2 cc. ampules containing 0.25 gm. (3¾ grains), or 0.5 gm. but it leaves the injected area painful for several hours. It is questionable whether its dubious benefit is sufficient to justify this discomfort. Some of the advocates of aminophylline combine this drug, given intravenously, with the hypodermic or intravenous administration of atropine.

After the most severe symptoms are controlled, aminophylline is sometimes continued orally, usually in doses of 0.2 gm. (3 grains) three times daily. To avoid gastric irritation the xanthines are usually prescribed in enteric-coated tablets or capsules taken after meals. Other xanthines used in the same way are theobromine in 5 grain or 7½ grain tablets or capsules, theobromine calcium salicylate (theocalcin) (7½ grain tablets—one or two, three to four times daily), theobromine sodium acetate (7½ to 10 grains in enteric-coated tablets or capsules). The theoretical benefit derived from these efforts at continuous coronary vasodilatation is questionable, but the xanthine drugs are widely used. Their continued administration in any individual case is justified only when repeated periods of use and withdrawal appear to indicate that they are definitely beneficial when taken.

Papaverine. This drug is an opium alkaloid which by relaxing smooth muscle dilates the coronary and peripheral arteries. Unlike morphine, it is only mildly sedative, not constipating and not habit-forming. It has been recommended for cases of myocardial infarction because of its dilator action on the coronary arteries, because it appeared to reduce the mortality following experimental coronary ligation in dogs,[69] and because it tended to abolish experimentally induced premature contraction and decreased the frequency of experimental ventricular fibrillation.[51] Like aminophylline it is also claimed to reduce cardiac pain by increasing the coronary blood flow.

Papaverine is most apt to be effective when administered intravenously

in doses of 60 to 90 mg. (1 to 1½ grains) diluted with 10 to 20 cc. of saline or distilled water, and repeated if necessary every two to three hours during the acute phase of the disease. Some physicians combine papaverine with aminophylline, both given intravenously, but great caution should be exercised lest they produce a sharp drop in blood pressure. As with aminophylline, papaverine should be injected very slowly when given intravenously. More conservative physicians give the drug hypodermically. In either event papaverine may be continued orally after the first few days, in doses of 0.06 to 0.2 gm. (1 to 3 grains) every four hours. The clinical claims for the usefulness of papaverine in acute myocardial infarction are, in my opinion, still unproven. Its intravenous administration appears especially unwarranted when the better established forms of therapy appear to be controlling the clinical course.

Nitrites. Nitrites should not be used in the treatment of acute cardiac infarction. Patients accustomed to the use of amyl nitrite or nitroglycerin for preceding episodes of angina pectoris often take these drugs at the onset of pain due to an acute myocardial infarction. Physicians also, under the mistaken notion that they are dealing with an episode of angina pectoris, may prescribe nitrites at the onset of cardiac infarction. Sometimes the failure of nitrites to relieve pain is the reason for summoning the physician or it is the first clue which suggests to the physician that he is dealing with a case of myocardial infarction and not angina pectoris. While such usage is occasionally unavoidable in doubtful cases, the nitrites are dangerous and should be avoided when there is any suspicion that the pain is caused by cardiac infarction. Although the nitrites are strong coronary vasodilators, they induce a further drop in the blood pressure which has already been depressed by myocardial infarction. This pronounced diminution in blood pressure may seriously reduce the coronary flow through the unoccluded vessels, in spite of vasodilatation. Fatalities attributed to their usage have been reported.

Sedatives and Soporifics. Sedatives are among the most widely used and most valuable drugs in the treatment of cardiac infarction. They are employed after subsidence of severe pain eliminates the need for morphine or similar opiates. In certain cases with little or very transient pain, sedatives and soporifics may be the only drugs required. *Phenobarbital* in doses of 30 mg. (½ grain) three times daily is commonly given to allay apprehension, anxiety or restlessness, and often causes mild drowsiness. It may also reduce the susceptibility to ectopic rhythms, especially ventricular tachycardia. It is often advisable to maintain the patient in a somewhat drowsy state during the first days of the acute illness. Phenobarbital may have to be supplemented by soporifics such as seconal 0.1 gm. (1½ grains), nembutal (pentobarbital) 0.1 gm. (1½ grains), barbital 0.3 gm. (5 grains), ipral calcium 0.12 gm. (2 grains). Sedatives and soporifics should not be given to the point of causing respiratory depression. In some patients the barbiturates cause excitement instead of depression, especially with large doses. Continued use may cause a dermatitis in susceptible individuals. As the patient improves, the dose of phenobarbital may be reduced to 15 mg. (¼ grain) three times daily.

Bromides 1 gm. (15 grains), or chloral hydrate 0.3 to 0.6 gm. (5 to 10 grains) alone or in combination with bromides, may be substituted or alternated with the phenobarbital. During the period of recovery, demerol for occasional or persistent moderate pain or codeine for milder pain, administered orally or hypodermically, may be combined with sedation.

Digitalis. Digitalis should be employed in the treatment of acute myocardial infarction only when there is congestive heart failure or an arrhythmia with very rapid ventricular rate. While there is general agreement as to the indication for digitalis whenever heart failure develops, many physicians avoid it when the heart failure is associated with acute myocardial infarction. Following is an evaluation of the objections, mostly theoretical, which have been raised to the use of digitalis in acute myocardial infarction:

(1) By increasing the force of cardiac contraction, digitalis, it is argued, may rupture the weak infarcted muscle or dislodge a mural thrombus. This purported danger implies that digitalis increases the intraventricular pressure. On the contrary, an increased diastolic pressure is produced not by digitalis but by cardiac failure.

(2) Because the ischemic myocardium is hyperirritable following acute coronary occlusion, it is feared that digitalis may increase this irritability and promote the probability of ventricular tachycardia and ventricular fibrillation. While digitalis has been known to cause extrasystoles, it has also diminished or abolished them. No justifiable conclusion can therefore be drawn that digitalis will cause this serious arrhythmia when given in therapeutic doses to humans. The basic reason for serious arrhythmias after coronary occlusion is the consequent myocardial anoxia; since digitalis improves the metabolic efficiency of the heart muscle, it may diminish rather than increase their frequency.

(3) It is feared that digitalis may further diminish the already depressed cardiac output which is associated with cardiac infarction and shock. But although digitalis reduces the cardiac output in health, it increases the cardiac output when heart failure is present (p. 174).

(4) Another objection to the use of digitalis after acute coronary occlusion is the belief that digitalis causes constriction of the coronary arteries. But the available experimental and clinical evidence is contradictory as regards this contention (p. 326).

(5) Recently another objection has been raised to the use of digitalis, based on animal experiments[54] and clinical studies which suggest that digitalis reduces the clotting time and increases the tendency to embolization.[17, 77] De Takats et al.[17] noted a shortening of the clotting time following the use of digitalis and claimed to have observed an increased incidence of thrombosis in cases treated with this drug. Massie et al.,[58] who observed a similar effect on the clotting time, attributed it to the presence of saponins in crude digitalis preparations. Other observers have been unable to find any change in the coagulation time in man caused by digitalis.[97] Whether these observations are sufficient to prohibit the use of digitalis in patients with cardiac infarction remains to be determined. The dosage required to reduce the coagulation time in animals was far in excess of human therapeutic levels. In humans digitalis neutralized the effect of heparin rather than producing a shortening of the coagulation time itself. The clinical cases presented to suggest a cause and effect relation between digitalis and thrombosis are unconvincing. In any event it has been reported that this effect of digitalis on the clotting time may be prevented by heparin and Dicumarol.[54, 17]

In the absence of more convincing objections it has been my practice to administer digitalis for the treatment of heart failure even in the first few days after myocardial infarction unless the heart failure is readily controlled by the

more immediate measures of bed rest, opiates, oxygen therapy and occasionally venesection. When heart failure is characterized by acute pulmonary edema, which does not respond to the above-mentioned measures, strophanthin may be given in the form of ouabain, beginning with 0.25 mg. intravenously and repeated in an hour if necessary. An additional 0.25 to 0.50 mg. may be given intravenously or intramuscularly twelve hours later. This drug should not be given if the patient has been receiving digitalis immediately prior to the attack. Other digitalis preparations for intravenous digitalization have been discussed (p. 187).

For less severe left ventricular failure characterized by persistent dyspnea or paroxysmal dyspnea, as well as for the fully developed symptoms and signs of right- and left-sided heart failure, with or without sinus rhythm, the patient should be digitalized in the manner previously outlined (p. 183). However, it has been recommended that because of the increased sensitivity of the infarcted myocardium to digitalis, the total dosage should approximate 25 per cent less than the usual dose.[103] As always the most important guide to digitalis dosage is the clinical response of the individual patient.

Mercurial Diuretics. These preparations (p. 194) are indicated chiefly in cases of acute cardiac infarction which are characterized by congestive heart failure from the very beginning, and in cases in which congestive heart failure becomes manifest after the patient resumes activity. They are less widely used, but also of striking benefit for the treatment of recurrent nocturnal paroxysms of cardiac asthma which may develop early after cardiac infarction.

Quinidine. Quinidine is employed during the treatment of acute cardiac infarction to combat the development of numerous and troublesome premature contractions, persistent auricular flutter and fibrillation without cardiac failure, and ventricular tachycardia (see below). There is no significant basis to justify its routine use for the purpose of preventing these arrhythmias.

Sulfonamides and Penicillin. These drugs are occasionally used in the treatment of acute myocardial infarction, either because there is a definite complicating pneumonia or because it is sometimes difficult to distinguish between extensive pulmonary congestion (especially when complicated by infarcts) and bronchopneumonia. Roentgenologic examination is not always feasible and does not easily distinguish between pulmonary infarction and pneumonia. If sulfonamides are given, potassium citrate or other potassium salts should be used for alkalinization in place of sodium bicarbonate to avoid fluid retention. In general it is preferable to administer penicillin in the form of crystalline procaine penicillin in an average single daily intramuscular dose of 300,000 units. Some physicians routinely prescribe sulfonamides or penicillin as a prophylactic if there is evidence of pulmonary congestion (moist râles at the bases) and fever, because of the frequency with which bronchopneumonia complicates pulmonary congestion, as well as because of the occasional difficulty in distinguishing the two conditions.

Insulin. The question of the use of insulin arises frequently because cardiac infarction is common in diabetics and because the risk of hypoglycemic shock is especially great for the ischemic myocardium. Hyperglycemia and mild transient glycosuria are fairly common after acute coronary occlusion; in themselves they are no indication for the use of insulin and they may not denote any more than potential diabetes (p. 440). On the other hand, insulin should be used in patients with uncontrolled diabetes, which is often intensified by the

occlusion, but the dosage should be such as to permit a mild glycosuria or at least a moderately elevated blood sugar as a margin of safety. In my experience in such cases, regular insulin, administered as needed according to the findings in fractional specimens, is preferable to and safer than routine orders of protamine zinc insulin.

Treatment of Complications

The management of cardiac shock (p. 481), acute pulmonary edema (p. 482) and other forms of congestive heart failure has been discussed above as the treatment of intrinsic manifestations of acute cardiac infarction rather than of complications.

Arrhythmias. Premature beats, usually ventricular, are common, rarely affect the prognosis, or require treatment. However, when ventricular premature beats recur frequently and cause subjective annoyance, quinidine may be administered (p. 279).

Ventricular Tachycardia. Quinidine is the drug of choice in its treatment, but potassium and magnesium salts and other drugs have been recommended (p. 285).

Auricular Fibrillation. Usually paroxysms of auricular fibrillation in the course of cardiac infarction subside spontaneously after several hours and thereafter require no treatment. When persistent, quinidine may be given in an effort to restore regular rhythm (p. 279). When auricular fibrillation is associated with congestive heart failure or a high ventricular rate, digitalis should be given according to the principles previously outlined (p. 183). Subsequently digitalis may be stopped temporarily and quinidine administered in an effort to restore sinus rhythm. Askey and Neurath[4] recommend the simultaneous administration of digitalis and quinidine when myocardial infarction is complicated by both auricular fibrillation and heart failure.

Embolism. Since *pulmonary embolism* arises almost exclusively from venous thrombi in the lower extremities, prevention of such thrombosis is more important than efforts at treatment after embolization occurs. This is discussed in detail elsewhere (p. 882).

Embolization of a Peripheral Artery. Embolectomy is the most important single therapeutic measure and promises restoration of circulation in a high percentage of cases if the operation can be performed within twelve hours after the occurrence of the embolism.[35, 87, 45, 67, 105] The results of embolectomy are rarely satisfactory, even as regards the restoration of circulation, if more than twenty-four hours have elapsed. However, Atlas[5] reported recovery of a patient operated upon successfully for an aortic embolus, sixty hours after its occurrence. As a rule, embolectomy is indicated when the embolus is situated at the bifurcation of the aorta, of the common iliac artery or of the femoral artery. But embolectomy is only occasionally or rarely necessary for embolization of the upper extremity or of the popliteal or more distal arterial branches of the lower extremity, because there is an adequate collateral circulation.[89] In the latter instances, an attempt at surgical removal of the embolus should be performed only if there is loss of function of the muscles supplied by the affected artery.

Although the ultimate outlook for patients with embolization is poor, with or without embolectomy, because of the serious underlying cardiac disease, many lives and more extremities could undoubtedly be salvaged by embo-

lectomy. Griffiths[34] found that 87 per cent of patients with arterial embolism who were not operated upon died within a fortnight and the remainder required a major amputation. On the other hand Key[40] reported 86 successful embolectomies in 216 cases. Strömbeck,[99] reporting on the late results of 327 embolectomies performed in Sweden, stated that 63 per cent died in the hospital, 18 per cent were discharged as improved after amputation, and 19 per cent recovered with restoration of the affected circulation. Of the latter group, three quarters were alive after one year, one half after three years, one third after five years, and one eighth after ten years. In 24 patients with embolic occlusion of an artery in one or more extremities, Reynolds and Jirka[89] operated on 18 limbs, in 16 of which the embolus was successfully removed and in 13 of which the circulation was restored. Nevertheless, 12 of the patients succumbed because of their underlying disease, despite successful removal of the embolus. While these figures are far from encouraging, the operation is justified even for the small percentage of lives or limbs that it is capable of saving, especially since it is accompanied by small risk. Even in cases of saddle embolus of the aorta, which is almost invariably fatal, recoveries have been reported following embolectomy.[5, 39] McClure and Harkins[67] collected 21 successful cases of aortic embolectomy.

The immediate treatment of peripheral arterial embolism includes the administration of opiates for the severe pain that is usually present; the inhalation of 100 per cent oxygen may also be tried. Heparin should be given intravenously if embolectomy is to be performed in order to prevent recurrent thrombosis at the operative site. Paravertebral lumbar sympathetic block is recommended for relief of associated arterial spasm and to improve the collateral circulation. Papaverine, administered intravenously, preferably in large doses of 1½ to 3 grains several times daily, has been recommended for the same purpose,[2] but its effectiveness has been questioned. However, Reynolds and Jirka[89] advise that sympathetic block and the use of antispasmodics should be postponed until after operation in cases in which embolectomy is to be performed, because of the danger that relief of arterial spasm may permit progression of the emboli to vessels from which they cannot be removed easily. Anticoagulant therapy with heparin or Dicumarol (p. 882) should be continued at least two or three weeks postoperatively. (For details of surgical technic, see McClure and Harkins[67] and Reynolds and Jirka.[89])

If embolectomy is not to be done, anticoagulants (heparin and Dicumarol) may be given to prevent enlargement of the embolus by local thrombosis. Paravertebral sympathetic block, papaverine and prostigmine may be utilized to promote the collateral circulation and relieve associated arterial spasm. Favorable results have been reported from the use of intermittent venous compression which restricts the venous flow without occluding the arterial circulation, and thus promotes the blood supply of the ischemic extremity. In cases which are seen late, that is after twenty-four hours, or in which the arterial wall is seriously damaged, an arteriectomy may be performed to prevent reflex vasospasm of the collateral vessels and propagation of thrombus. When there are evidences of beginning gangrene, refrigeration of the extremity may be tried. With the development of gangrene, amputation is usually necessary.

Diabetic Acidosis. Although diabetic acidosis and coma complicating acute cardiac infarction may be difficult to control because of the active cardiac process, the general principles of controlling diabetic acidosis should be fol-

lowed. Parenteral fluids and insulin should be administered promptly and in sufficient amounts to control hyperacetonemia, dehydration and shock. Whatever one's opinion may be as to the advisability of including glucose in the parenteral fluids in the usual case of diabetic coma, it appears safer to do so when the latter complicates cardiac infarction. The danger of hypoglycemic shock must be avoided and if the acidosis is controlled, insulin should not be pressed to the point of completely abolishing glycosuria and hyperglycemia. One should also avoid the danger of precipitating pulmonary edema by giving excessive quantities of fluid, especially fluids containing sodium. The necessity of hospitalizing patients with acute myocardial infarction and diabetic coma for continuous observation and frequent physical and laboratory examinations appears obvious.

Periarthritis of Shoulder and Disturbances of Hand. Pain and disability of the shoulder and arm and trophic disturbances of the hand usually run a protracted course and are resistant to treatment. As a rule, the shoulder-arm symptoms subside spontaneously after three to twelve months or longer depending on their severity. Diathermy, roentgen ray therapy, procaine infiltration of local trigger zones and various physiotherapeutic and orthopedic measures have been employed with uncertain effect. Adequate analgesics or even occasional opiates are required for relief of pain and should be administered. Motion should be encouraged as tolerated, but not to the point of pain; active manipulation should be avoided. Stellate ganglionectomy, upper dorsal sympathetic blocks with procaine or surgical dorsal sympathectomy has been recommended by Steinbrocker and his associates.[98]

Convalescence and Rehabilitation

The duration of convalescence and the decision as to whether and when a gainful occupation may be resumed must be determined individually in each case. Patients with pronounced and persistent symptoms of congestive heart failure, with angina pectoris recurring frequently at rest or after minimal effort, or with extreme weakness may require an indefinitely prolonged period of convalescence. It is often necessary to adjust the patient to the necessity of indefinite or permanent retirement from work or business, and psychotherapy becomes a dominant element in medical management.

The physician should not enforce prolonged invalidism merely because the patient has experienced a severe attack. Nor should the patient be led to believe that chronic invalidism is the inexorable consequence of myocardial infarction even if the symptoms do not permit a complete restoration of previous activity. The physician must assess the comparative merits of a miserable enforced invalidism, of which the effect on longevity is questionable, against a less confined but happier life which may involve slight theoretical risks.

Patients who recover from the acute attack and who experience little or no distress as they become ambulant should nevertheless spend a variable period after recovery in gradually resuming normal care of themselves in the home and short walks outdoors. When this is accomplished, a holiday of two weeks or longer is often desirable to induce a philosophic and psychologic readjustment.

The resumption of physical exertion after convalescence often presents a problem. Many patients complain of weakness and experience dyspnea on moderate exertion. Careful evaluation is necessary to determine whether these symptoms are the consequence of extensive myocardial infarction and conges-

tive heart failure; if so, limitation of physical exertion must be continued and treatment designed to improve the cardiac and circulatory status. On the other hand, these symptoms are often the consequence of inactivity, poor muscular tone and other related disturbances which go under the heading of lack of training. Under these circumstances, fatigability, weakness and dyspnea on exertion may be best managed by graduated exercises and the gradual resumption of muscular activity. At least a fair trial should be made to determine whether the response to such a graduated regime is favorable or not. Sometimes fear and anxiety associated with the knowledge of having suffered a heart attack leads to an almost neurotic timidity of any physical effort. The need for reassurance and explanatory discussions is obvious.

Economic as well as medical considerations often dictate the extent to which the patient can modify his type of work, the conditions and hours of his employment, periods of rest and vacations. In some instances through the effort of individuals, in others through the work of various local heart associations, the cooperation of employers has been enlisted in finding suitable work for patients who have suffered an acute cardiac infarct. These activities should be broadened and extended.

Self-employed business and professional men should be persuaded to obtain an assistant or to delegate more and more of the less important and especially the more strenuous and time-consuming duties to other associates. The objective should be the elimination of severe physical exertions, of prolonged hours of work, of emotional tensions, of excessive duties, of the pressure of deadlines or of work which does not permit reasonable and regular hours for meals, relaxation and vacations.

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PART IV

STRUCTURAL ABNORMALITIES OF THE HEART

22

ACUTE PERICARDITIS

Pericarditis is an inflammation of the enveloping membranes of the heart, i. e., the visceral or parietal pericardium or both. It is almost always a part of, secondary to, or a complication of some other disease. It may be the result of a bacterial infection or a manifestation of some general disease such as rheumatic fever. Pericarditis may represent the sole cardiac lesion or it may develop in combination with myocarditis, endocarditis or both. Diagnostically, the term pericarditis is itself incomplete; whenever possible, the etiologic agent or disease should be determined and expressed.

The *incidence of pericarditis* of all types, based on necropsies, has been given as between 4 and 12 per cent[98, 120] and that of acute pericarditis between 2 and 7 per cent[60, 81] of all autopsies. The incidence of pericarditis as determined clinically is much lower, for some cases produce no significant symptoms and a great many with symptoms are undiagnosed.

CLASSIFICATION AND ETIOLOGY

Pericarditis may be classified etiologically according to the causative bacterial agent, when known, or according to the disease of which it is a part or a complication. The following etiologic varieties of pericarditis have been noted:

1. Rheumatic pericarditis
2. Tuberculous pericarditis
3. Bacterial pericarditis (pneumococcus, streptococcus, staphylococcus, etc.)
4. Uremic pericarditis
5. Pericarditis secondary to myocardial infarction
6. Pericarditis due to malignant neoplasm
7. Traumatic (usually bacterial) pericarditis
8. Pericarditis of Libman-Sacks disease
9. Actinomycotic pericarditis
10. Syphilitic (gummatous) pericarditis
11. Pericarditis associated with parasitic disease, especially echinococcus and cysticercus
12. Pericarditis of undetermined etiology

Pericarditis has been classified pathologically according to the type of pericardial reaction and exudate. The following are the most common forms: fibrinous pericarditis, serofibrinous pericarditis, hemorrhagic pericarditis,

purulent or suppurative pericarditis and adhesive pericarditis. Combinations of the above are not infrequent. Pericarditis has been classified also into certain clinical-pathologic groups, usually: (1) acute fibrinous pericarditis, (2) pericarditis with effusion, (3) chronic adhesive pericarditis, (4) constrictive pericarditis.

PATHOLOGY

Fibrinous Pericarditis. This is characterized by a proliferation and desquamation of the lining endothelial cells of the pericardium, by a fibrinous exudate on its surface and by degenerative and inflammatory changes in the collagen tissue of the epicardium. There may be degenerative and necrotic alterations in the subepicardial myocardium which have been held responsible for the electrocardiographic abnormalities often observed in acute pericarditis. The development of a pericardial granulation tissue leads to healing and scar formation. This may produce various degrees of adhesion of the pericardial layers with partial or complete obliteration of the pericardial cavity.

Serofibrinous Pericarditis. The pathology is similar to that of fibrinous pericarditis except there is a greater fibrinous exudative reaction and an outpouring of serous fluid because of a more severe or extensive pericardial injury. These pericardial effusions vary from 100 to 1000 cc. but occasionally exceed 2 liters. The normal quantity of pericardial fluid varies between 15 and 30 cc. and should not exceed 50 cc. The effusion is usually straw colored, but may be turbid because of desquamated endothelial cells, lymphocytes and polymorphonuclear leukocytes. It has the characteristics of an exudate, i. e., a high protein content (over 3 per cent), a specific gravity above 1.018, and yields a positive Rivalta reaction. The pericardial effusion of congestive heart failure is a transudate.

The effusion usually resorbs in a week or two in cases of rheumatic pericarditis, but may persist for months or years in nonfatal cases of tuberculous pericardial effusion. Frequently adhesive pericarditis results. Bacterial pericarditis may begin as a fibrinous or serofibrinous pericarditis and later become purulent. I have seen sterile serofibrinous exudates of an acute type following relatively mild infections of the upper respiratory tract. Although the pericarditis of uremia and myocardial infarction is usually of the (dry) fibrinous type, it may be associated with serofibrinous effusions.

Hemorrhagic Pericarditis. This is a variant of serofibrinous pericarditis in which the effusion contains sufficient blood to give it a grossly hemorrhagic appearance. It is observed most commonly in tuberculous, neoplastic or lymphoblastomic pericarditis, but may occur in other types, especially those of long duration. Hemorrhagic pericarditis is to be distinguished from hemopericardium (p. 520).

Purulent Pericarditis. This is a pericardial inflammation due to pyogenic organisms and characterized by a pus-containing effusion, usually less than 250 cc. in amount, but varying between 10 cc. and a liter or more. The pus is not foul. Occasionally sacculated effusions develop. Adhesions between the pericardial layers and the neighboring structures are common.

Rarely *chylopericardium* is observed, in which a milky pericardial effusion results from obstruction of the thoracic duct due to neoplasm[128] or due to trauma.[5] Pericardial effusions rich in cholesterol have also been reported

(cholesterol pericarditis).[62] In Alexander's[2] case the fluid had the appearance of gold paint.

CLINICAL FEATURES

Subjective Symptoms

There are three groups of symptoms: (1) pain or precordial distress, (2) dyspnea and other symptoms resulting from compression of the heart and adjacent thoracic structures and (3) general symptoms due to the pericardial inflammation or to the general disease of which the pericarditis is a part.

1. Pain. Precordial pain has long been considered a characteristic symptom of acute pericarditis, but it is probably absent as often as it is present. When pain occurs, it may be sharp and severe or dull and vague. It is usually situated over the precordium, but it may radiate to the left shoulder, neck and arm, to the epigastrium and to the left scapular region and thus simulate the pain of coronary occlusion. When the pain is exclusively abdominal, an acute abdominal complication may be erroneously diagnosed, the thoracic origin of the pain being entirely overlooked. The pain is often intensified by deep inspiration, by movement of the chest wall and by cough, observations which suggest a relationship to involvement of the costal or diaphragmatic pleura.

The *pathogenesis of pain in pericarditis* has been greatly clarified by the experimental studies of Sutton and Lueth[107] on dogs, and especially by studies in human beings in whom the pericardium was punctured for aspiration or exposed during and after cardiac surgery.[20, 3] The visceral pericardium is entirely insensitive to pain. But Capps[20] found that puncture of the lowermost left lateral portion of the parietal pericardium at the level of the fifth or sixth intercostal space causes pain which is referred to the left side of the neck. The parietal pericardium at higher levels was found to be insensitive to pain. Capps concluded that pain fibers from the phrenic nerve are present only in the lower part of the parietal pericardium. In a patient with a therapeutic opening in the pericardium, Porter[80] found that only the anterior surface of the parietal pericardium was sensitive to pain. The observations of Alexander and his associates[3] differed somewhat from those of Capps.[20] They found none of the pericardium sensitive to heat or cold. There was only an awareness of pressure when pressure was made on the inner surface of the posterior or left posterolateral wall of the parietal pericardium. However, there was severe local and referred pain when pressure was made on the inner surface of the anterior parietal pericardium and chest wall. Similar pain was elicited by pinching this part of the pericardium or by sweeping the finger around the pericardial surface.

While the pathogenesis of the pain associated with pericarditis is not completely elucidated, the following mechanisms appear to be concerned, according to the extensive studies of Capps:[20]

(a) Pericardial effusion may produce a dull oppressive pain (protopathic pain) by distention of the entire pericardial sac and therefore of the pain-sensitive lower parietal pericardium.

(b) An associated (contiguous) pleuritis of the diaphragmatic, costal or mediastinal pleura, and not the pericarditis, occasions the pain. This accounts for the occurrence of sharp pain and for pain with distant radiations outside of the neck.

(c) Myocardial ischemia and not an associated pericarditis accounts for pain in cases of coronary thrombosis with myocardial infarction.

2. Dyspnea and Other Compression Symptoms. Dyspnea is an early, frequent and usually the most prominent symptom in cases of pericarditis with effusion. Objective manifestations are a rapid respiratory rate, shallow and forced respirations and the extreme orthopneic position assumed by the patient.

The pathogenesis of the dyspnea is uncertain since there is usually no physical or roentgenologic evidence of pulmonary congestion. Only occasionally are râles heard at the bases of the lungs. The absence of pulmonary congestion may be due to interference with the inflow of blood into the right side of the heart and consequently into the pulmonary circulation (see cardiac tamponade below). It is likely that the dyspnea results, at least to some extent, from actual mechanical compression of the bronchi or lungs and, in cases of huge effusions, from the diminished vital capacity caused by encroachment on the available thoracic space. This mechanical explanation of dyspnea is consistent with the observation that patients with pericardial effusions are somewhat or moderately relieved by leaning far forward (in contrast to those with pulmonary congestion who merely elevate the head and shoulders) so that the effusion is shifted down from the base of the heart and anteriorly against the chest wall.

Occasionally other symptoms besides dyspnea are produced by compression of the trachea, bronchi, lungs and esophagus. There may be a dry hacking cough, hoarseness or dysphagia. These symptoms are most apt to occur in cases with very large effusions, such as are encountered most often with tuberculous pericarditis.

3. General Symptoms. General symptoms may be due to the pericardial infection or inflammation as such or to the general disease with which the pericarditis is associated. *Fever,* sweating, chills, fatigability or weakness, loss of weight, anxiety, depression or delirium may be present, according to the etiology of the pericarditis.

Objective Signs

The objective evidences of acute and subacute pericarditis are: (a) changes in physical signs in the chest due to inflammation of the pericardium and the presence of an effusion, (b) manifestations of altered circulatory dynamics due to cardiac tamponade or compression caused by elevated intrapericardial pressure and (c) general manifestations of the pericardial inflammation and the associated disease.

Physical Signs in the Chest. *1. Pericardial (Friction) Rub.* A pericardial rub is conclusive evidence of an acute pericarditis. This is a superficial, scraping, scratchy or grating sound or ocasionally one with a coarse leathery quality. There are usually to-and-fro sounds which phonocardiograms disclose are due to vibrations set up during ventricular and auricular systole, and occasionally also during the phase of rapid ventricular filling, early in diastole.[31]

The pericardial rub is usually heard in the pulmonic area or just to the left of the lower sternum, fairly well localized to a small area. Its location may shift with a change in the patient's position. It is best heard if the patient leans forward and moderate pressure is made on the chest wall with the bell of the stethoscope. The pericardial rub is often very evanescent; it may be audible for a few hours at a time and intermittently for a few days; occasionally it persists for weeks or even months.

A pericardial rub is usually associated with a dry fibrinous pericarditis. However, as recognized long ago by Stokes,[104] a pericardial rub is often heard also in the presence of a pericardial effusion. Conner[28] noted a friction rub in 24 out of 34 cases of pericarditis with effusion. While a pericardial rub is a sign of either an acute fibrinous pericarditis or a pericarditis with effusion, the following signs are elicited only in the presence of a significant effusion.

2. Increased Width of Cardiac Dullness at the Base of the Heart. The left border of cardiac dullness in the second and third left interspace is significantly shifted to the left. This results in a widened area of dullness at these levels, especially with the patient in the recumbent position. This area of dullness becomes definitely narrower if the patient sits up, since the effusion settles lower because of gravity.[64]

3. Generalized Increase in Cardiac Dullness. When there is a considerable pericardial effusion, percussion reveals a generalized enlargement of the area of cardiac flatness, which assumes a globular shape if the patient is recumbent. There may be a characteristic rapid increase or decrease in the area of flatness during the course of the disease. There is a sharp transition along the left border from pulmonary resonance to cardiac flatness without the intermediary of relative cardiac dullness.

4. Ewart's or Pins' Sign. In cases with large pericardial effusions, there is often a patch of dullness below the angle of the left scapula, occasionally extending one third or more of the way over the left lower posterior chest wall. Over this dull area there is bronchial breathing and usually also bronchophony or egophony. Râles are usually absent although occasionally a few scattered moist râles may be heard. While these signs were observed earlier, their significance was stressed first by Pins,[77] the Viennese, and later by Ewart,[36] whose name is now attached to this sign in English-speaking countries. Ewart's sign is due to compression of the base of the left lung by the pericardial effusion which extends posteriorly. This explanation has been disputed,[23, 59] but in my opinion remains the most plausible.

5. Other Physical Signs. Numerous other physical signs of pericardial effusions have been described, but they are either less specific and less constant than those mentioned above, or of doubtful value.

The cardiac impulse is often weak and wavy or may disappear entirely. Similarly the heart sounds are usually muffled and distant, especially when the patient is recumbent. However, I have several times felt a strong apical impulse and heard loud heart sounds in the presence of significant pericardial effusions.

There may be a distinct increase in cardiac dullness to the right of the sternum in the fifth intercostal space (Rotch's sign).[90] But percussion is often unreliable in this area and the dullness may be obscured by compensatory emphysema.

Cardiac Tamponade. The term cardiac tamponade or acute cardiac compression denotes an interference with the diastolic filling of the heart and with cardiac contraction due to an increase in intrapericardial pressure. This occurs in many cases of pericarditis with effusion, as well as in cases of acute hemopericardium.

Hemodynamics of Cardiac Tamponade. The following hemodynamic changes in cardiac tamponade have been observed experimentally[39, 84, 27, 99, 5] following the injection of fluids under pressure into the pericardium of dogs,

and in clinical studies of human cases of pericardial effusion[102, 119] and hemopericardium.[119]

(1) There is a reduction in the stroke output and later in the cardiac output per minute as well. (2) There is a progressive rise in the right intra-atrial and venous pressure as the pressure within the pericardium rises. (3) The cardiac rate increases. (4) The arm-to-tongue circulation time is prolonged. (5) The vital capacity diminishes. (6) There is a late fall in blood pressure, especially in the systolic pressure.

The stroke output diminishes because the elevated pericardial pressure compresses the right atrium and interferes with the venous inflow from the great veins. The rise in venous pressure helps to maintain filling, but the concomitant rise in atrial pressure diminishes the effective filling pressure difference. The rise in venous pressure is a measure of the disparity between the venous return and the ability of the heart to accept and expel that return. Venous infusions may increase the venous and right atrial pressure and thereby restore the normal cardiac output or increase it.[29, 38]

A normal cardiac output is temporarily maintained by a compensatory tachycardia, probably effected by the elevated venous and right atrial pressure through the Bainbridge reflex. The blood pressure is at first maintained by peripheral vasoconstriction. But at a critical level of intrapericardial pressure (100 to 150 mm. saline) there is a sharp drop in stroke and cardiac output and the blood pressure falls. The pulse pressure diminishes because of a greater reduction in the systolic pressure. If the intrapericardial pressure is reduced by paracentesis these circulatory abnormalities are reverted more or less toward normal.

In clinical pericarditis with effusion, as in the experimental form, the development of cardiac tamponade depends on the rise in intrapericardial pressure;[123] the latter is determined by the quantity of the effusion and its speed of formation. A very acute effusion of 150 to 250 cc. (in hemopericardium or suppurative pericarditis) can cause tamponade, while slowly developing effusions of a liter or more (tuberculous effusions) may be tolerated if the pericardium is given time to distend and the pressure is only slightly elevated.

Clinical Manifestations of Cardiac Tamponade. 1. An *acute compression triad* has been stressed by Beck[10] and consists of a rising venous pressure, a falling arterial pressure and a small quiet heart. The latter is best observed by fluoroscopy. Tachycardia is also a prominent manifestation. If the cardiac output is greatly reduced, there is a fall in blood pressure and a clinical picture of shock. In cardiac tamponade associated with rapidly formed but relatively small effusions, the physical signs of (large) pericardial effusion, described above, are absent.

2. *Systemic venous congestion* occurs with subacute or chronic tamponade due to effusions which develop more slowly. In these cases a compensatory increase in circulating blood volume may tend to maintain the cardiac output, but later causes systemic congestion. *Engorgement of the cervical veins, increased venous pressure* and *enlargement of the liver* are the usual manifestations. Compression of the venae cavae may result in increasing cyanosis of the lips, face and neck and occasional facial edema. If the cardiac output falls sharply during the stage of venous congestion, the clinical picture of shock may be added to that of congestive heart failure.

3. *Paradoxical pulse*[58] is an almost constant manifestation of cardiac tam-

ponade. There is a *distinct* diminution in pulse amplitude during inspiration. This may be revealed more clearly by a fall in blood pressure of 10 to 20 mm. Hg or more, at the end of inspiration.

Normally there is a tendency to paradoxical pulse, because the slightly increased venous return during inspiration is more than outweighed by the greater volume of blood accommodated in the chest. Therefore, at full inspiration, the cardiac stroke output from the left ventricle and consequently the pulse and blood pressure are diminished. In cases of pericardial effusion or other causes of cardiac compression, this phenomenon is intensified as follows: The increased venous return during inspiration cannot be translated into an increased cardiac output because of the pericardial obstruction to inflow. On the other hand the increased pulmonary vascular capacity during inspiration diminishes the venous return to the left heart. The combination of impaired venous inflow and the enhanced pulmonary capacity and retention of blood during inspiration cause the reduction in left ventricular output and in size of the pulse (paradoxical pulse). A pulsus paradoxicus may also be observed in cases of tracheal obstruction and other conditions associated with exaggerated respiratory excursions and therefore with an abnormal increase in pulmonary vascular capacity during inspiration. Other explanations have been offered by Wenckebach[121] and by Gauchat and Katz.[43]

Inspiratory swelling of the cervical veins commonly accompanies pulsus paradoxicus in cases of pericardial effusion (and constrictive pericarditis), but is absent when the pulsus paradoxicus is due to laryngeal stenosis, etc. The cervical veins swell because the increased venous return during inspiration cannot be handled by the compressed right atrium with its high intra-atrial pressure. Normally the increased venous return is adequately received and ejected without permitting a rise in venous pressure or venous distention.

General Signs. Fever, sweating, weakness and loss of weight have already been mentioned. A polymorphonuclear leukocytosis is usually present, its severity in proportion to the height of the fever. In cases of tuberculous pericarditis, however, there is usually a relative leukopenia or normal white blood count, even with moderate fever. Very marked leukocytosis and polynucleosis suggests a bacterial suppurative pericarditis. In rheumatic pericarditis pallor and anemia are often prominent features.

The *general appearance* of the patient with pericardial effusion is noteworthy. He is anxious, suffering, restless, cyanotic or pale and assumes a characteristic posture. Usually he sits up completely and leans far forward. This differs somewhat from the orthopneic position of the patient with congestive heart failure, who is usually relieved by merely elevating the head or head and chest. Rarely the patient assumes the knee-chest position (signe de la prière Mahométane); this is observed also in occasional cases of mediastinal neoplasms or lymphomata.

Roentgenology

Roentgenologic examination may suggest or confirm the presence of a pericardial effusion.[40] Its value is greatly increased if serial films are taken at brief intervals and if the patient is examined in both the recumbent and upright (or sitting) positions. Roentgenologic abnormalities, like the abnormalities in physical signs, depend essentially on the size and distribution of the effusion and not on the intrapericardial pressure. It is doubtful whether effusions of less

than 250 cc. in adults produce a significant effect on the cardiopericardial silhouette. But in infants and children 150 cc. or less may suffice to alter the shadow. The following are the most valuable roentgenologic signs (Fig. 56):

1. The well-demarcated normal outlines of the individual cardiac chambers and great vessels are obliterated, resulting in a smoothening of the cardiac bor-



Fig. 56. Pericarditis with effusion. Upper, before paracentesis. Lower left, after paracentesis, with air injected into pericardial space. Lower right, after recovery seven and a half months later.

ders with loss of the angular curves. In particular, the waist of the silhouette on the left border (pulmonary arterial segment) is filled out to give a straight or slightly convex left cardiac outline. A pear-shaped or water-bottle type of silhouette results.

2. The vascular supracardiac shadow becomes shortened and somewhat widened due to the filling of the superior recess in front of the great vessels by fluid.

3. The posterior inferior recess (as viewed in the right anterior oblique or lateral view) is normally demarcated by a straight line or one that is slightly

concave posteriorly. When an effusion forms, the fluid encroaches early on the clear space in this recess and the straight or concave line becomes a bulge which is convex posteriorly.[75]

4. *There is a marked diminution or almost complete absence of visible pulsations of the heart.* A wavy undulation may replace the alternating contraction and relaxation. The diminution or absence of pulsation may be more clearly demonstrated by roentgenkymography or electrokymography.

5. Serial roentgenograms may reveal rapid changes in the size of the silhouette corresponding to a speedy increase or resorption of the effusion (Fig. 56).

6. Induction of pneumopericardium following aspiration of the pericardium is helpful in distinguishing pericardial from pleural effusion as well as in revealing the size of the cardiac shadow[37] (Fig. 56). Sacculated effusions may occur, chiefly in suppurative, rheumatic[122] or chronic pericarditis, and localize in regions where cardiac motion is least active, e. g., near the great vessels or along the lower right border. These sacculated collections of fluid may produce a localized bulge, usually on the right cardiac contour, and must be differentiated from aneurysm of the aorta or sinus of Valsalva, a pericardial diverticulum, pleural or mediastinal effusions, or benign pericardial tumors. Pericardial effusion may be differentiated from cardiac enlargement by the disappearance in the former of the intersections between vascular, cardiac and diaphragmatic contours on the right and the atrioventricular contour on the left, by absence of the changes in size and shape of the silhouette during the Valsalva and Müller maneuver which persist with cardiac enlargement, and by disappearance of the bronchial bifurcation.[6]

7. Angiocardiography reveals a characteristic shadow due to fluid surrounding the opacified cardiac chambers.[122a]

The Electrocardiogram

Distinctive electrocardiographic abnormalities were observed by Winternitz and Langendorff[124] in 46 (61 per cent) of 76 cases and by Bellet and McMillan[11] in 80 per cent of 57 cases. Similarities to the changes in myocardial infarction may indicate that the electrocardiographic abnormalities of acute pericarditis are actually due to associated subepicardial myocardial lesions,[48, 117, 11] or, less likely, to myocardial ischemia caused by cardiac tamponade.[51]

The various electrocardiographic changes occurring in cases of acute pericarditis include the following:[93, 117, 124, 49, 68, 114]

1. RS-T Changes. The most consistent and significant electrocardiographic alteration in acute pericarditis is an elevation of the RS-T segment in all three standard leads, in leads I and II, in leads II and III, or in lead I. If the RS-T segment is elevated in leads I and II or lead I alone, it is not depressed in lead III; if it is elevated in leads II and III, it is not depressed in lead I (Fig. 57). Thus the reciprocal elevation and depression of the RS-T segment in leads I and III, which are characteristic of myocardial infarction, are not found in acute pericarditis.

The RS-T segment differs from that seen in myocardial infarction in that it runs obliquely upward in a straight line or with an upward concavity to a positive T wave.[92] In cases of myocardial infarction with RT elevation, this segment shows an upward convexity. However, in later stages of acute peri-

carditis when the T wave becomes negative, the RS-T segment may show an upward convexity as with acute myocardial infarction.

Since the elevation of the RS-T interval may last as briefly as three days and rarely more than three weeks, this abnormality is usually not observed later in the course of the disease. Harvey and Whitehill[46] and others failed to note an elevation of the RS-T segment in their cases of tuberculous pericarditis, which were usually seen more than a month after the onset of symptoms. But in two cases of tuberculous pericarditis seen by Holzmann[49] in the first eight days of the disease and in a third seen on the fourteenth day, there were elevations of the RT segment in two leads. Similar changes were observed by Bellet and McMillan[11] in 2 out of 20 cases.

In precordial leads also, there may be an elevation of the RT segment or inversion of T waves.[11, 118]

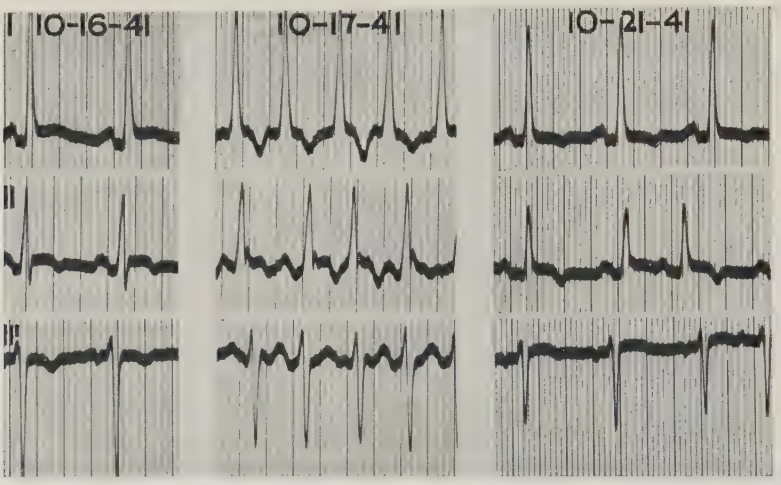


Fig. 57. Acute and subacute pericarditis in bacterial endocarditis. Progressive changes. RT elevations in leads I and II followed by T wave inversions.

2. T Wave Changes. The T wave undergoes progressive flattening as the RS-T segment returns to the isoelectric line (Fig. 57). The upward concavity of the ST segment disappears. During this stage Winternitz and Langendorf[124] have also noted a double T wave, a delayed T wave and a linear oblique drop from the R to the T wave.

Several weeks after the onset of the pericarditis, the T wave becomes inverted. Diagnostically, an inversion in all three of the standard leads is most significant. More often the T waves are inverted in leads I and II or in leads II and III. At this stage the ST segment may be curved convexly upward and lead into a sharply inverted T wave resembling the cove-plane "coronary T wave" of myocardial infarction.[73] This was first reported in a case of rheumatic pericarditis of Porte and Pardee[79] and in various forms of pericarditis by Peel.[74]

The inversions of the T wave persist longer than the RS-T changes, but they usually revert to normal within two to three months. In chronic cases of tuberculous pericarditis, inverted T waves may persist throughout the course of the disease.

3. Diminution in QRS Voltage. A diminution in the voltage of the QRS

complex was noted as a sign of pericardial effusion by Oppenheimer and Mann,[71] who suggested that it was due to short circuiting of the electrical impulses of the heart by the surrounding fluids. Low voltages of the QRS and T waves are in themselves insufficient evidence of myocardial or pericardial disease. Low voltage of the QRS complex as well as negativity of the T wave is especially frequent in cases of tuberculous pericarditis. This electrocardiographic abnormality cannot be well correlated with the size of the pericardial effusion, for Harvey and Whitehill[46] noted that following aspiration of a tuberculous effusion, the voltage of the QRS complex diminished almost as often as it increased.

The duration of the QT interval is not prolonged as it is in most cases of congestive heart failure, a distinction of diagnostic value.[113]

Differences in Electrocardiograms of Pericarditis and Myocardial Infarction. The following are the chief distinctions: (1) The RS-T elevation in pericarditis occurs without the reciprocal RS-T depression in leads I or III seen in myocardial infarction. (2) The T wave in pericarditis may be inverted in all three standard leads; this is rare with myocardial infarction, unless both aspects of the heart are involved. (3) The positive initial deflection in chest leads is rarely absent with pericarditis, often absent with acute myocardial infarction. (4) Q waves are rarely significant in the standard leads of cases with acute pericarditis; a deep Q_1 or Q_3 commonly accompanies a negative T in the same lead in cases of acute myocardial infarction. In combined anterior and posterior infarction there may be an elevation of the RS-T segment or an inversion of the T-waves in all standard leads as in acute pericarditis,[126] but there is often also a deep Q_1 or Q_3 and the positive initial deflection in the chest lead is usually absent.

When pericarditis complicates myocardial infarction, there may be an early elevation of the RS-T segments in the standard leads indicative of the pericarditis followed by the characteristic pericardial inversion of the T-waves, but often disappearance of the RS-T elevation is succeeded by the typical deep Q_1 and negative T_1 or deep Q_3 and negative T_3 of myocardial infarction (see p. 443).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

To diagnose acute pericarditis one must be aware of the possibility of this complication in those conditions which are most often associated with it. Precordial pain and fever, unexplained dyspnea and tachycardia, evidence of systemic venous congestion, without apparent heart disease, should suggest a search for acute pericarditis. A pericardial rub, characteristic water-bottle enlargement of the heart, Ewart's sign,[36] a paradoxical pulse, extreme diminution of cardiac pulsations and the characteristic electrocardiographic changes are the most important diagnostic features. Aspiration of the pericardial sac may serve both to confirm the diagnosis of pericarditis and to determine the etiologic type. Stained smears and cultures of the aspirated fluid should be made and some of the fluid may have to be inoculated in guinea pigs if tuberculosis is suspected.

Diagnostic difficulty may occasionally arise in distinguishing acute pericarditis from cardiac enlargement of undetermined origin, from congestive heart failure, from pleuropulmonary disease, from valvular heart disease when the rub is confused with a murmur, from myocardial infarction because of pre-

cordial pain and somewhat similar electrocardiographic changes,[8, 127, 26] from acute abdominal complications when the pain radiates to the abdomen, and from aneurysm or tumor when there is a sacculated effusion. Angiocardiography is helpful in distinguishing some of these conditions.

COURSE AND PROGNOSIS

The course and prognosis of acute pericarditis are determined usually by the disease of which it is a complication, e. g., rheumatic fever, uremia. Suppurative and tuberculous pericarditis usually have a progressive course and fatal outcome, but these may be favorably altered by antibiotic and surgical therapy. This is discussed further under purulent pericarditis (p. 517) and tuberculous pericarditis (p. 517).

TREATMENT

As a rule treatment is directed toward the underlying disease and not the pericarditis per se. Occasionally the pain of pericarditis is severe enough to require codeine or morphine for relief during the very acute phase. In cases of rheumatic pericarditis, full doses of salicylates usually relieve the pain and hasten the resorption of the pericardial fluid (p. 759). I have long discarded the traditional ice cap recommended in the treatment of painful pericarditis. The sulfonamides and antibiotics are indicated in the treatment of pyogenic bacterial pericarditis. Occasionally recovery is attributed to such drugs alone, administered intrapericardially as well as intramuscularly or intravenously.[96, 44, 125, 129] But as a rule surgical drainage of the pericardium must be performed (infra). Recovery from acute tuberculous pericarditis may follow streptomycin therapy.[61a]

Pericardial Aspiration

Indications. Aspiration of the pericardium is performed (a) to confirm the diagnosis of pericardial effusion, (b) to determine the etiologic agent or (c) to relieve symptoms of cardiac compression.

In rheumatic pericarditis, pericardial aspiration may be necessary if there is extreme dyspnea and the effect of salicylates is not rapid enough. I have had to remove as much as 1200 cc. at one time but usually the removal of 200 to 400 cc. provides relief. If the diagnosis of suppurative pericarditis is reasonably certain, it may be preferable to institute prompt surgical drainage without previous aspiration. But the latter may be necessary to relieve acute cardiac tamponade or to prove the diagnosis. In cases of tuberculous pericarditis aspirations may be performed for treatment, as well as for diagnosis.

Site of Pericardial Aspiration. The following are the sites most commonly entered for pericardial aspiration. Roentgenograms should be available to aid in determining the most favorable site.

1. The fifth left intercostal space, about 2 cm. inside the left border of percussion dullness, is the site most commonly used. If there is a distinct apical impulse, the needle may be introduced 1 or 2 cm. lateral to the impulse.

2. The angle between the xiphoid process and the left costal arch is the site recommended when there is a large effusion and the lower portion of the pericardial sac is to be drained. It is often used for aspirating suspected purulent effusions because in this region the lung does not cover the heart.

3. The right fourth intercostal space, 1 cm. medial to the right border of

cardiac dullness, is the site used when most of the pericardial effusion seems to be sacculated on the right side. I have had more than a liter of fluid removed through this site in a patient with rheumatic pericarditis after only a few cubic centimeters could be obtained by the first mentioned approach.

4. The seventh or eighth left intercostal space posteriorly in the midscapular line, the left arm of the patient being elevated to remove the scapula, is the site employed when there are evidences of a large effusion with pulmonary compression (Ewart's sign[36]) and fluid cannot be obtained readily elsewhere. This site of aspiration has been especially recommended by Conner[28] and by Sutton.[106] It should not be used in cases of suspected purulent pericarditis because of the danger of infecting the pleura.

Technic of Pericardial Aspiration. Pericardial aspiration is performed with precautions as to surgical asepsis. The exact site of insertion of the needle and the subcutaneous tissue are anesthetized with 2 per cent procaine solution. A 3 inch aspirating needle of 18 to 16 gauge with short bevel, connected directly or through a connecting piece of tubing to a 20 or 30 cc. syringe, is inserted through the anesthetized area between the ribs until it is felt to penetrate the resistant pericardial membrane. Usually this occurs at a depth of 3 to 5 cm. If the posterior site is chosen, a 4 inch needle should be used, as the pericardium may be penetrated at a depth of 5 to 8 cm. from the skin surface. If the effusion is thick, a trocar may have to be substituted for the needle in order to avoid blocking the lumen.

When the needle is inserted into the left fifth intercostal space, it is directed inward and backward toward the spine; when inserted in the left xiphoid costal angle, it is directed backward, upward and slightly inward; when inserted in the right fourth intercostal space, the needle is directed backward and medially toward the spine; when inserted posteriorly, the needle is directed forward and somewhat medially.

Gentle suction is made by withdrawing the barrel of the syringe. If a free flow of fluid is not obtained, the needle should be tilted carefully in various directions, withdrawn slightly, or carefully inserted somewhat more deeply. If no fluid is obtained despite these maneuvers and there is reasonable certainty as to the existence of a pericardial effusion, the needle should be inserted in one of the other sites mentioned. Sometimes a two-way or three-way stopcock is placed between the aspirating needle and syringe, so that no air will enter the pericardium and the fluid may be discharged into a container without disconnecting the syringe. If large quantities of fluid are to be removed, the needle may be connected by tubing to a bottle containing a partial vacuum as in performing a thoracentesis for pleural effusion.

Occasionally the needle is felt to come in contact with the heart. There is little danger from perforation of the ventricular wall, but the needle should be withdrawn slightly if cardiac pulsation is felt. Rarely one may cause a hemopericardium by cutting a coronary artery or perforating the thin-walled auricle. Other dangers of pericardial aspiration include injury of the internal mammary artery and the infection of pleura or peritoneum in cases of purulent pericarditis.

Surgical Drainage

If the diagnosis of purulent pericarditis is fairly certain, or has been proven by pericardial aspiration, adequate drainage should be obtained by surgical incision. Appropriate sulfonamide and antibiotic therapy should be given.

Numerous surgical approaches have been suggested including a transsternal, right or left parasternal, chondroxiphoid, or a combination of transsternal and left parasternal. Often, exposure of the pericardium is effected in the region along the left side of the lower sternum where the pericardium is not covered by lung. This is known as the interpleural space or triangle of safety. After the superficial tissues are reflected, the fifth, sixth and if necessary the seventh left costal cartilages are resected and sometimes also a portion of the adjacent sternum.[94] Bigger[13] resected the fourth and fifth left costal cartilage and Bunch,[19] the sixth. In general, the site of exposure should be as low as possible in early cases. Ross[89] prefers a chondroxiphoid approach, i. e., through the angle between the xiphoid process and left costal margin. He splits the rectus muscle to reach the pericardium from below in order to obtain dependent drainage from the oblique pericardial sinus posterior to the heart. In late cases of pericarditis, especially with large effusions, a posterolateral approach is utilized[112] because of the accumulation of fluid in the posterior recesses behind the heart. The seventh rib is resected near the midaxillary line. Because of adhesion of the pericardium to the pleura in the cases reported, it was possible to perform a pericardiotomy without producing a pyopneumothorax.

Drainage may be maintained with the aid of rubber tubes or tissue, extending down to but not into the pericardial cavity. Irrigation with warm normal saline is employed if drainage is unsatisfactory or if the patient fails to do well. Two drainage tubes should be inserted if irrigation is employed so that one of the tubes may permit egress of the fluid injected through the other. Otherwise, the injected fluid may be trapped and may cause cardiac tamponade. Some surgeons suture the opened pericardium to the soft parts and do not use rubber or other drains.

After drainage has been established, it is important to look for and drain purulent foci elsewhere (especially empyema or osteomyelitis). The persistence of fever, even after pericardiotomy, should always suggest the possibility of empyema, an undrained sacculation of pericardial fluid or a suppurative focus elsewhere.

INDIVIDUAL FORMS OF PERICARDITIS

Rheumatic Pericarditis

This is probably the most common type of pericarditis and is part of a rheumatic pancarditis. Its clinical features are discussed in the chapters on rheumatic fever.

Uremic Pericarditis

This occurs in the end stages of renal insufficiency as noted by Bright[18] and emphasized by Taylor.[110] Pathologic studies reveal a pericarditis in 8 to 45 per cent of cases of nephritis.[83, 7, 50] In the presence of uremia, regardless of etiology, pericarditis probably occurs in more than 50 per cent of cases.

The pericarditis is usually of the dry, fibrinous type but there may be a sterile serofibrinous or hemorrhagic effusion.[83, 7] Not infrequently there is a terminal, secondary bacterial infection. The development of uremic pericarditis has been related to metabolic chemical alterations in the blood. Healing and the formation of fibrous adherent pericarditis occur in those patients who survive several weeks after onset of the pericarditis.

The pericarditis is asymptomatic and its diagnosis is made by discovering a pericardial rub which is occasionally heard in the left interscapular region[21] as well as in its more common precordial location. Death usually occurs within one to three weeks after onset of the pericarditis[83] but survival for months is not as uncommon as is generally believed.[7, 53]

Bacterial (Purulent) Pericarditis

This is one of the commonest forms of pericarditis.[81, 98, 14, 1] The causative organisms are usually the staphylococci, the pneumococci and hemolytic streptococci, but a variety of other microorganisms are occasionally responsible, including the meningococcus[72, 100] and P. tularensis.[103]

A purulent pericarditis arises (a) by direct extension of an intrathoracic infection, (b) by hematogenous bacterial dissemination, (c) by traumatic introduction of bacteria through the chest wall, or (d) occasionally by extension or perforation of the diaphragm from a subdiaphragmatic suppurative focus, such as a liver abscess.[130] Osteomyelitis, staphylococcal or streptococcal sepsis, pneumococcal or streptococcal empyema, especially of the left pleural cavity, are common preceding diseases. Bacterial pericarditis may be fibrinous at its onset and then serofibrinous or serohemorrhagic before it becomes purulent.

The clinical features of purulent pericarditis are obscured by those of the general or local primary disease. Fever, leukocytosis and toxemia are common. Unexplained dyspnea, with or without cyanosis, cervical venous engorgement, a falling blood pressure and weak rapid pulse are indicative of purulent pericarditis especially in the presence of the usual causative conditions. The presence of a pericardial rub is diagnostic. Electrocardiographic changes (RT segment elevations) and fluoroscopic evidence of pericardial effusion or of minimal cardiac pulsation are confirmatory.

The mortality of practically 100 per cent for medically treated cases of suppurative pericarditis has been reduced to between 25 to 50 per cent by instituting surgical drainage.[112, 95, 105] The combination of chemotherapy, antibiotics and early surgical drainage (p. 515) will undoubtedly further reduce mortality. Recovery depends on simultaneous adequate surgical and medical therapy of other suppurative foci as well as the pericarditis.

Tuberculous Pericarditis

This occurs in about 1 per cent of all autopsies[55] and in about 3 to 7 per cent of those on tuberculous subjects.[108, 76] There is a striking predilection for males, and for the aged.[111, 22, 4] But it may occur in young adults or in children.[16, 78]

Pathogenesis. Tuberculous pericarditis arises by contiguous extension of tuberculous lesions of the hilar or mediastinal lymph nodes, or of pleuropulmonary tuberculosis.[47] There may be direct contact,[52] or infection of the pericardium may result from retrograde lymphatic extension. More rarely tuberculous pericarditis results from hematogenous dissemination, but the pericarditis is usually an insignificant element in the generalized miliary tuberculosis. Although pathologically tuberculous pericarditis is always secondary to tuberculous lesions elsewhere, clinically it may appear as the sole or primary manifestation.[85, 111, 24, 78, 101,

Pathology. The pericarditis starts as an acute fibrinous reaction which is followed by a subacute or subchronic stage of effusion and pericardial thicken-

ing. The thickening is due to the development of tubercles, caseous masses and connective tissue. Even in the chronic stage characterized by fibrosis there may be large persistent collections of serofibrinous or hemorrhagic fluid, or occasionally cheesy pus. Eventually the pericardial layers become adherent to each other and to the myocardium or neighboring structures and may cause constriction of the heart (p. 529). Calcification of the pericardium may appear.

Clinical Picture. The clinical picture is often vague and usually overlooked. The onset is insidious, with symptoms such as weakness, fatigability, loss of weight, anorexia and low grade fever.[35] *Cough* may be a prominent and early feature but expectoration and hemoptysis are uncommon. Precordial pain may or may not be present and is rarely as severe as with rheumatic pericarditis. There may be a friction rub in the early stages of the disease. This may last from two days to three weeks.[52] Fever may be absent but usually it is high and swinging.[46]

When an effusion develops, as it almost always does, the patient suffers from *dyspnea* and other evidences of circulatory embarrassment. Due to cardiac compression, the cervical veins become engorged, the venous pressure elevated, the liver enlarged and there may be subcutaneous edema and ascites. A pronounced tachycardia is common. The clinical picture may simulate that of congestive heart failure or chronic constrictive pericarditis.[9] In the acute and subacute stages the clinical picture may be that of a chronic wasting disease with unexplained pyrexia. There may be physical signs of a pericardial effusion. Pleural effusions are commonly associated.[52, 47] Auricular fibrillation and partial heart block have been noted.

Diagnosis. The diagnosis involves recognition of the pericarditis and determination of the tuberculous etiology. It should be considered in cases of unexplained fever and/or congestive heart failure, especially in elderly males who present no evidence of cardiac disease. The diagnosis of pericarditis may be supported by the presence of a pericardial rub, paradoxical pulse, and roentgenologic signs of pericardial effusion and inverted T waves in the electrocardiogram.

The etiologic diagnosis can be made only by aspirating the pericardial effusion and discovering the organisms in the centrifuged specimen, or by determining their presence through inoculation of a guinea pig. If a hemorrhagic effusion or one of very large size (over 1000 cc.) is obtained, a tuberculous etiology is suggested. After aspiration an artificial pneumopericardium may be produced by the injection of air and a small heart demonstrated roentgenographically.[12] This and the absence of murmurs and of leukocytosis help to differentiate tuberculous from rheumatic pericarditis with effusion.

Prognosis. The outcome is generally unfavorable, death occurring in three to six months.[47, 46] Recovery has been reported in 15 per cent or more.[45, 35] Death usually occurs from cardiac failure or miliary tuberculosis. Of 24 proven cases observed by Blalock and Levy,[15] 4 were alive at the time of their report. In 3 of these 4, a pericardiectomy had been performed.

Treatment. Rest in bed and general supportive measures are necessary during the acute stage. Analgesics or narcotics may have to be administered if pain is severe. Repeated aspirations may have to be performed but only when these are necessary to relieve dyspnea or severe systemic congestion. Generally half as much air is replaced as the amount of fluid removed.[121, 70] If constrictive pericarditis develops, pericardiectomy (decortication) is performed only after

the tuberculous process becomes inactive. However, occasionally in such cases it is necessary to operate even during tuberculous activity if the patient's condition grows steadily worse and the venous pressure rises despite the fact that the pericardial-cardiac shadow decreases in size.[15]

Other Forms

Pericarditis in Acute Myocardial Infarction (p. 420, 437).

Pericarditis due to Malignant Neoplasms. This is almost always due to extension of primary or secondary malignancies of the thoracic organs, especially carcinoma of the lungs or breast, to the pericardium. There is usually an effusion which is serofibrinous or hemorrhagic, but which may become purulent because of secondary bacterial infection. Further discussion may be found in the chapter on neoplasms of the heart (Chapter 45).

Traumatic Pericarditis (Chapter 44).

Pericarditis in Libman-Sacks Disease (p. 556). Clinically this is only occasionally revealed by a pericardial rub. At postmortem examination I have observed a macroscopic, a local or diffuse fibrinous or serofibrinous pericarditis or a dense universal adhesive pericarditis in 14 out of 23 cases of this disease. Massive pericardial effusion, responsible for clinical symptoms, has been noted in 2 cases.[33]

Actinomycosis of the Pericardium (p. 844).

Parasitic Disease of the Pericardium (p. 847).

Roentgen-ray therapy has produced pericardial inflammation or a chronic massive pericardial effusion when employed in a case of hyperthyroidism[88] and in a case of carcinoma of the breast, respectively.[17]

Acute Benign Pericarditis. A benign form of acute pericarditis, usually with effusion, has been reported by a number of observers,[66, 67, 97, 30, 61] and I have observed several similar cases. The effusion is sterile and the etiology unknown although Rinzler and Leibowitz[87] reported isolation of the hemolytic streptococcus in their case. The disease has been noted chiefly in young adults and shortly after a mild infection of the upper respiratory tract. The initial pain and electrocardiographic abnormalities may simulate acute myocardial infarction.[109, 61] The disease subsides spontaneously within a few weeks but occasionally produces an adhesive pericarditis.

PERICARDIAL DIVERTICULA

Certain pericardial outpouchings or diverticula are really chronic, encapsulated pericardial effusions, resulting from pericardial inflammations. Occasionally they are tuberculous.[41] These diverticula are sometimes referred to as cysts or herniations of the pericardium. Pericardial diverticula may also represent congenital anomalies, e.g., in the case of Yater[128] in which the cyst was interpreted as arising from a lymphatic vessel in the pericardium.

There are usually no subjective symptoms. Occasionally there are chest pressure or pain or other complaints, which may not be due to the diverticulum as such. Rarely the diverticulum points anteriorly and may present as a nontender rounded mass on the anterior chest wall near the sternum.[34, 41]

The diagnosis of pericardial diverticulum is made by roentgenologic examination, as pointed out by Kienböck and Weiss.[54] The diverticulum appears as a sharply outlined or lobulated semicircular, oval or polygonal area protruding from the cardiac silhouette, usually from its lower right contour, occasionally

from its left side. It may or may not pulsate. Pulsations present on one examination may disappear after a period of years. Calcification may develop over many years' observation.[54]

HEMOPERICARDIUM

Hemopericardium denotes the accumulation of blood in the pericardial cavity. It should be distinguished from conditions in which pericardial inflammation produces a hemorrhagic exudate as in tuberculous or malignant pericarditis. However, inflammation of the pericardium may complicate hemopericardium, e.g., when the latter is due to the entrance of an infected foreign body.

The *etiology* of hemopericardium is varied.[42] Essentially, it results from rupture of the wall of a cardiac chamber, a coronary artery, the aorta or rarely the pulmonary artery. These structures are either diseased or torn by trauma. Hemopericardium may also be due to scurvy, leukemia or other hemorrhagic diseases.

The commonest cause of acute hemopericardium is *acute myocardial infarction* due to coronary artery occlusion. The softened ventricular wall is most likely to rupture in the first ten days after the infarction. According to Fulton,[42] one eighth of the deaths in the first three weeks after an acute myocardial infarct are due to rupture of the ventricle and acute hemopericardium. Rupture of the left ventricle is about seven times as common as that of the right, and that of the anterior wall three times as frequent as that of the posterior according to Krumbhaar and Crowell.[56] The auricles of the heart may also rupture and cause hemopericardium as a result of myocardial infarction.[25] Spontaneous rupture of the heart with hemopericardium may result from involvement by malignant tumors, cysts or myocardial abscesses due to bacterial endocarditis.

Rupture of the aorta, in its intrapericardial portion, with consequent hemopericardium may be the result of (1) syphilitic aneurysm, (2) arteriosclerosis or medionecrosis (so-called spontaneous rupture of the aorta, see p. 818), (3) adult coarctation of the aorta with rupture just above the aortic valve,[82] and (4) mycotic aneurysms burrowing along the aorta into the pericardial cavity.

The coronary artery may rupture and bleed into the pericardial sac usually as a result of trauma but also when the vessel wall is weakened by periarteritis nodosa (necrotizing arteritis[116]) or by arteriosclerosis.[69]

Trauma of the heart and pericardium[32] is considered elsewhere (Chapter 44). Perforation of the ventricle and acute hemopericardium results most often from stab wounds or bullet wounds of the chest wall. Occasionally a blunt injury to the chest wall may cause infarction and rupture of the heart or rupture of a coronary artery with secondary hemopericardium.[65] Rarely the myocardium or coronary vessels are torn during pericardial paracenteses, surgery of the pericardium or sternal puncture.[91]

The pathologic physiology and clinical picture are essentially those of cardiac tamponade (p. 507). The degree and rapidity of bleeding are important. Occasionally, as with malignant tumors, there may be a slow oozing with chronic cardiac compression. Usually bleeding is rapid and cardiac tamponade occurs with as little as 250 cc. blood in the pericardium. There may be sudden death occurring within one hour after rupture of a ventricle. Not infrequently hours or days elapse, during which the picture of acute cardiac compression develops (p. 508), characterized by high venous pressure, a falling arterial pressure and

a small quiet heart. Shock is frequent. Other manifestations are determined by the different causes of hemopericardium.

The *diagnosis* is made by the history and examination, which may reveal the etiologic factor, and by the evidences of acute cardiac compression denoting the pericardial effusion. The fluoroscopic signs and electrocardiographic changes are those described under pericarditis with effusion (p. 509) and cardiac trauma (p. 982).

The prognosis is usually poor, due not only to the hemopericardium, but to the primary disease. In cases of trauma, the prognosis is good if the diagnosis is made early and treatment instituted promptly.

Treatment of the hemopericardium per se consists of relief of acute tamponade by pericardial aspiration or, if time permits, by surgical removal of the hemorrhagic collection followed by suture of the rupture or closure by graft. Transfusions and other measures to combat shock are important. (See also cardiac trauma, p. 983.)

HYDROPERICARDIUM

Hydropericardium denotes an excessive quantity of transudate in the pericardial cavity. It is probable that the normal amount of pericardial fluid is not more than 30 cc., but amounts up to 50 cc. are not regarded as excessive. Hydropericardium is to be distinguished from pericardial effusions resulting from pericarditis.

Hydropericardium is usually part of a generalized anasarca of congestive heart failure or glomerulonephritis. It also occurs in myxedema, in cases of occidental beriberi, in the rare cases of scleredema or Buschke's disease,[115] or terminally in wasting diseases such as tuberculosis or carcinomatosis, even when there is no direct pericardial involvement. It may be part of a nutritional deficiency with hypoproteinemia. Hydropericardium may result from local causes which interfere with the venous return from the pericardial circulation, such as mediastinal tumors, tumors of the lung or heart, mediastinal lymphomata or tumors of the thymus or mediastinal lymph nodes.

The amount of fluid may vary from 100 to several thousand cubic centimeters. As a rule, there is no interference with cardiac action and no subjective symptomatology. Rarely, large effusions occur and may require aspiration to relieve cardiac tamponade.

PNEUMOPERICARDIUM

Pneumopericardium, or the presence of air in the pericardial cavity, is uncommon. In 1925 Rigler[86] found 73 reported cases including 1 of his own. Often the air is associated with fluid, which is usually of a purulent nature—pyopneumopericardium.[63]

Pneumopericardium results from (1) traumatic perforation, (2) perforation of a neighboring air-containing organ into the pericardium[45a] or vice versa, (3) artificial introduction of air into the pericardium either intentionally or accidentally, and (4) possibly by spontaneous formation of gas when the pericardium is infected by gas-producing bacilli.

When infection by gas bacilli causes air to be present within the pericardial tissue itself, the condition is termed pneumatosis of the pericardium.

Usually there are no subjective *symptoms* of the pneumopericardium or they

are masked by the more serious consequences of the causative condition. Occasionally cardiac compression is produced. If there is a large quantity of air there may be tympany on percussion of the precordium and metallic or clinking heart sounds on auscultation. If both fluid and air are present, characteristic loud, gurgling or splashing metallic sounds may be audible (bruit de Moulin). There may also be a pericardial rub.

Radiologic examination readily reveals the presence of air which is indicated by a laterally delineated area of increased transparency around the cardiovascular silhouette. There is usually striking cardiac activity. There may be a horizontal fluid level which moves with cardiac pulsations.

Treatment may be unnecessary, as small quantities of air are readily absorbed. Usually treatment must be directed to the more serious primary or associated conditions. When these can be satisfactorily treated, it may also be necessary to aspirate the pneumopericardium or to provide surgical drainage of a pyopneumopericardium.

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23

ADHESIVE PERICARDITIS. CHRONIC CONSTRICTIVE PERICARDITIS

Adhesive pericarditis denotes the presence of adhesions between the two pericardial layers, between the pericardium and heart or between the pericardium and various neighboring thoracic structures. Since chronic inflammatory changes are often absent, the term adherent pericardium is sometimes used instead of adhesive pericarditis. The terms fibrous pericarditis or fibrosis of the pericardium may be used when scar tissue with or without active inflammation is present in the pericardium but there are no concomitant adhesions. Adhesive pericarditis of varying degree was found in 1.6 per cent of 8912 necropsies at the Mayo Clinic[65] and in 2.26 per cent of 1900 necropsies at Massachusetts General Hospital.[68]

Concretio cordis (internal adhesive pericarditis) denotes adhesion, usually extensive, between the parietal layer of the pericardium and the visceral layer (epicardium). There may be partial or complete obliteration of the pericardial cavity.

Accretio cordis denotes the adhesion of the pericardium to neighboring extracardiac structures. It is often associated with internal adhesive pericarditis with or without cardiac compression. *Mediastinopericarditis* is a form of external adhesive pericarditis in which there is extensive scarring of the mediastinal structures with adhesion to a thickened pericardium.

The lesions known as *milk spots* or *soldiers' patches* are milky white, occasionally cloudy, irregular or oval flat plaques of hyalinized fibrous tissue. They are usually situated on the anterior surface of the right ventricle where it is not covered by lung. The large plaques occur singly; smaller ones may be multiple. They are found in about one third of hearts from childhood to old age, but occur with progressive frequency in older age groups.

One theory holds that milk spots result from mechanical tension or rubbing, perhaps against the anterior chest wall, during cardiac contraction. The alternative theory maintains that they are scars of healed pericarditis. Nelson[53] described villi, cellular exudation and other changes in 15 to 20 per cent of milk spots, suggesting a transition from a more active inflammatory process. Milk spots occur oftener in chronic valvular disease, coronary sclerosis and enlarged hearts than in normal hearts. But they cause no clinical manifestations and are unrecognizable during life.

INTERNAL ADHESIVE PERICARDITIS (CONCRETIO CORDIS)

This is essentially a pathologic lesion without clinical manifestations. It may result from any one of the varieties of acute pericarditis of which it represents the healing stage or end result.

The scar tissue in concretio cordis differs pathologically from the compression scar of constrictive pericarditis in that the former is thinner, less dense, contains many more capillaries and relatively fine wavy collagen fibers which do not impede cardiac relaxation and contraction.[1] Since rheumatic fever is the commonest cause of internal adhesive pericarditis,[65] the heart is frequently enlarged, not because of the pericardial adhesion, but because of the associated valvular and myocardial disease. On the other hand normal cardiac size is often observed in nonrheumatic cases of concretio cordis.[16, 43]

EXTERNAL ADHESIVE PERICARDITIS (MEDIASTINOPERICARDITIS)

This results from organization of the various forms of acute pericarditis, although uremia and myocardial infarction rarely produce external adhesions. The latter arise most often when the pericarditis is secondary to or associated with inflammation of adjacent thoracic structures. Rheumatic fever, tuberculosis and other intrathoracic infections, especially pneumonia and empyema, are the commonest causes of external adhesive pericarditis. External adhesive pericarditis is often associated with internal adhesion of the pericardium and occasionally with constrictive pericarditis.

Pathology

External pericardial adhesions result from the organization and fibrosis of fibrinous exudates. These adhesions, which may be long or short, thin and friable or very dense and firm, attach the parietal pericardium to the pleura, the diaphragm, the sternum and ribs or to most of the surrounding mediastinum. The term *callous or indurative mediastinopericarditis* has been applied to a densely adherent fibrotic mediastinum and pericardium. This may be indistinguishable from or associated with a constrictive pericarditis (pericardial compression scar), but the clinical abnormalities due to the latter must not be attributed to the external adhesions.

Pathologic Physiology

In a series of experiments conducted by Beck[2] during which intrapericardial and extrapericardial adhesions were formed, there was no indication of circulatory embarrassment, dilatation, hypertrophy or failure of the heart. In over 1000 subsequent experiments, during which various neighboring tissues were grafted onto the pericardium in order to provide a new blood supply to the heart, Beck and Tichy[6] produced adhesions which caused little or no cardiac disturbance. Only an acute angulation of the heart from its normal axis or a clockwise or counterclockwise torsion on its long axis was followed by cardiac disturbance and changes in arterial and venous pressure. Hosler and Williams[38] conducted a series of controlled experiments in which they produced intrapericardial, extrapericardial or combined intra- and extrapericardial adhesions to the diaphragm in dogs. In one instance the pull of the adhesions was so great as to cause sacculation of the right ventricle. Subsequently the dogs were exer-

cised regularly on a treadmill for two years. They observed neither circulatory disturbances nor macroscopic or microscopic evidence of cardiac hypertrophy.

In humans with external adhesive pericarditis (with or without obliteration of the pericardial cavity), there is no definite evidence that the adhesions cause either circulatory disturbance or cardiac hypertrophy. As with intrapericardial adhesions, the problem is complicated by the great frequency of rheumatic fever as the cause of external pericardial adhesions and by the consequent frequency of associated cardiovalvular disease. In cases of external adhesive pericarditis secondary to pulmonary-pleural or lymph node tuberculosis or to other pulmonary infections, I have never seen either circulatory disturbance or cardiac hypertrophy, except in occasional instances of cor pulmonale when there was extensive associated pulmonary disease. Similarly, combined external and internal pericardial adhesions usually cause no circulatory abnormalities or cardiac hypertrophy in cases of Libman-Sacks disease. In a review of 4400 necropsies, Hosler and Williams[38] reported 76 cases of extensive pericardial adhesions, which they did not segregate into internal and external forms. In the 54 cases with cardiac hypertrophy, there was invariably concomitant cardiac or vascular disease which could account for it. In the 21 cases in which the hearts were of normal or less than normal size there was no associated valvular disease. Thus the presence or absence of cardiac hypertrophy in adhesive pericarditis appears to be correlated entirely with the presence or absence of cardiovalvular or vascular disease and not with the adhesions.

Clinical Features

Symptoms. Symptoms rarely, if ever, result from external adhesive pericarditis. When there are clinical disturbances, they may be adequately explained by the associated cardiac or valvular disease.

Physical Signs. *1. Systolic Intercostal Retraction.* This occurs most often in the intercostal space near the apex, and occasionally in other parts of the precordium. Instead of the normal outward systolic pulsation (apical impulse), the intercostal space is drawn inward during systole. It was presumed to result from the tug of an external adhesion on the chest wall during systolic shortening of the heart. Friedreich[31] pointed out that the same phenomenon is observed in hearts without adhesions, particularly when there is enlargement secondary to aortic valvular disease. It is now generally believed that the retraction results from a partial vacuum created during systolic contraction of the heart, the effect being particularly noticeable when the heart is large.

According to Dressler[25] the systolic retraction is due to internal, not to external adhesions. He believes that these adhesions prevent the normal change in shape and elevation of the heart during systole and the consequent apical thrust against the chest wall. Retraction of the chest wall is due to the uncompensated aspirating effect of cardiac contraction.

2. Broadbent's Sign.[11] This is a special form of visible systolic intercostal retraction noted in the left posterior chest, at the level of the eleventh and twelfth ribs. It is believed to denote the presence of external pericardial adhesions in the region of the attachment of the diaphragm. But as the Broadbents[10,11] themselves have noted, cardiac hypertrophy without adhesive pericarditis may be associated with this sign. Furthermore, Broadbent's sign is relatively rare, even in cases of adhesive pericarditis.

3. Diastolic Shock. A palpable shock or propulsion during diastole may accompany the rebound of the retracted portion of the chest wall. Brauer[9] showed that even after removal of the overlying cartilages and ribs with their adhesions, this diastolic shock persists. Apparently it is not due to the adhesions.

4. Wenckebach's Sign.[77] This sign has been applied to different phenomena. There may be a lagging in elevation of the left nipple during deep inspiration, presumably because pericardial adhesions to the chest wall interfere with expansion of the left side of the chest. Wenckebach's sign[77] also refers to the observation that while the upper sternum expands anteriorly during deep inspiration, the lower sternum because of pericardial adhesions remains fixed or may even be retracted.

5. Fixation of the Position of the Heart with Change in Body Position. Normally the apex of the heart shifts 3 to 4 cm. as the body is turned from the right to the left lateral position. Fixation of the heart by external pericardial adhesions is said to cause diminution or absence of this shift. This sign may or may not be found in cases of external adhesive pericarditis, and it may be associated with marked cardiac enlargement without pericardial adhesion.

Other Signs. A *diastolic collapse of the cervical veins* (instead of the normal systolic collapse) was described by Friedreich[31] as a sign of adhesive pericarditis. But Riegel's[57] careful graphic records failed to confirm this. Friedreich's findings may have been explained by the presence of an associated tricuspid insufficiency which causes a positive venous pulse (see p. 620), i.e., collapse during diastole.

Paradoxical pulse (p. 508) and inspiratory swelling of the cervical veins were described as signs of external adhesive pericarditis,[44] but actually do not occur unless there is an associated constrictive pericarditis with impairment of venous inflow.

Roentgenology. Most of the changes attributed to external adhesions may be better explained by the usually associated cardiac enlargement or pleuropulmonary disease. However, abnormal elevation of the cardiac shadow and immobility or paradoxical motion of portions of the diaphragm may be due to adhesions. There may be isolated or continuous streaks, rings or plaques of calcification along the border of the pericardial cardiac silhouette.[84] Gluing of the arch of the aorta to the trachea by fibrous tissue may cause an elevation of the arch during swallowing, which is visible on fluoroscopy.

Electrocardiogram. This is usually of little diagnostic value. There may be no change in the electrical axis of the heart with change in body position.[24] Often the normal change in electrical axis is present.[60, 30]

Diagnosis

The demonstration of pericardial calcification roentgenologically is a certain diagnostic sign of adhesive pericarditis. But this sign fails to differentiate between external and internal adhesive pericarditis, and it may be present with or without constrictive pericarditis (cardiac compression). The value of all other signs is questionable, except that roentgenologic evidence may be suggestive of the presence of external adhesions.

Treatment

Brauer[9] reported a surgical procedure which was designed to free the heart from the alleged excessive work necessitated by the systolic tug of cardioperi-

cardial adhesions on the relatively rigid chest wall. The operation consists of resection of the cartilages and portions of the adjacent third, fourth and fifth ribs, and sometimes part of the lower sternum. Any readily accessible external adhesions on the anterior pericardial surface are divided. Brauer[9] referred to this operation as cardiolysis, although this term is more properly reserved for the procedure of pericardial resection utilized in the treatment of constrictive pericarditis (p. 537).

Although there is no cogent evidence that external pericardial adhesions contribute to the production of circulatory symptoms, many surgeons have reported favorable results with Brauer's[9] operation. Smith and Liggett[64] collected 107 operated cases from the literature and reported on the subsequent course as revealed to them by correspondence with the surgeons. Despite their favorable conclusions, neither the immediate nor subsequent results approached in brilliance those obtained with pericardial resection for constrictive pericarditis.

The following points must be considered in interpreting the reported results. (1) In most cases the bed rest and other therapeutic measures carried out in connection with the operation and postoperatively were more thorough than those employed before the decision to operate.[3] (2) The natural course of the disease led to coincidental spontaneous improvement. (3) In occasional cases with extremely large hearts, resection of the chest wall by enlarging the confining space may have permitted greater diastolic relaxation of the heart and thereby greater compensation for the cardiovalvular defects. In such cases the value of the operation is related to its effect on the enlarged heart and not on the external pericardial adhesions.

CONSTRICTIVE PERICARDITIS

(Pericardial Compression Scar)

Definitions

Chronic constrictive pericarditis[52] is a dense fibrous thickening of the pericardium, usually of uncertain but sometimes of tuberculous or other bacterial origin, which causes chronic compression of the heart and interferes with its diastolic relaxation and filling. This results in systemic venous engorgement and a diminished cardiac output, which produce a characteristic clinical picture. Because the disease is due to an external mechanical impediment without significant concomitant myocardial or valvular lesions, surgical removal of the fibrous pericardial encasing membrane is capable of effecting a rapid and sometimes brilliant result.

The term *Pick's disease* or syndrome is sometimes applied to cases of constrictive pericarditis. Pick[55] described a series of cases characterized by recurrent or progressive ascites, attended by little or no edema, in which postmortem examination revealed adhesive pericarditis and an atypical cirrhosis of the liver and fibrosis of its capsule. However, it is doubtful whether Pick's cases represent an homogeneous group.

Polyserositis or *Concato's disease*[18] has sometimes been used interchangeably with constrictive pericarditis. Concato referred to cases in which multiple serous cavities were presumed to be involved by tuberculosis. In my opinion it is questionable whether Concato's disease is an entity. Constrictive pericarditis differs essentially from the usual forms of polyserositis in that it is caused by

cardiac compression, while inflammation of the serous membranes is usually absent or occurs only secondarily.

Etiology

1. In most cases the cause remains uncertain even after microscopic and bacteriologic examination of the compression scar.

2. Tuberculosis is the commonest cause in cases of known etiology, but it accounts for only about 15 per cent of the cases.[36, 34]

3. Bacterial pericarditis, especially that due to the pneumococcus, occasionally results in constrictive pericarditis. Constrictive pericarditis has been reported due to P. tularensis.[40]

4. Rheumatic fever very rarely if ever causes constrictive pericarditis.

5. Occasionally there is a previous history of acute pericarditis, usually of undetermined etiology. There are reports of constrictive pericarditis appearing many months or years after an acute pericarditis.[26, 32]

6. Neoplastic involvement of the pericardium[76, 28] or a foreign body[74] in the pericardium may produce the syndrome of constrictive pericarditis.

Relationship of Tuberculosis. The highest incidence of tuberculosis in the resected pericardial scar was encountered by Burwell and Blalock.[12] Of 19 cases of constrictive pericarditis, 11 were proven to be tuberculous by microscopic examination, while 5 others were almost certainly due to tuberculosis although this could not be proven absolutely. Of 36 cases studied by Beck,[4] tuberculosis was demonstrated in the excised scars of 7; in 2 others there was tuberculosis elsewhere in the body but not in the scar. Of 22 cases reported by Schmieden and Westermann,[62] most were regarded as tuberculous or as "metastatic suppuration" following rheumatic arthritis. Of 15 cases studied by White[79] 2 were definitely due to tuberculosis (2 others were possibly tuberculous), 2 were due to pneumonia with polyserositis and 1 to sepsis; 10 were of unknown etiology. (See also Andrews et al.[1])

Relationship of Pyogenic Bacterial Infection. Burwell and Blalock[12] reported that aside from the above-mentioned 16 tuberculous cases of constrictive pericarditis in their series of 19, 2 of the remaining 3 were caused by the Staphylococcus aureus and the third was also believed to be of pyogenic origin. Of White's[79] 15 cases, 2 were secondary to pneumonia and 1 to sepsis. Isolated case reports have also indicated a history of pneumonia in patients in whom a constrictive pericarditis subsequently developed. Beck[4] stated his belief that constrictive pericarditis resulted from an infection which entered the pericardium from the pharynx, lungs, pleura or mediastinum.

Age and Sex. Constrictive pericarditis is essentially a disease of youth, although it may occur in persons beyond middle life. Most of the proven cases occur between the ages of ten and forty.

There is a preponderance of males over females in a ratio of about 3 to 1.

Pathology

The essential pathologic feature of constrictive pericarditis is a dense, callous thickening of one or both layers of the pericardium. Usually it is 3 to 5 mm. in thickness, but it may be 1 cm. or more. It has been described as being as hard as shoe leather. The thick pericardium forms an inelastic casement of armor composed of cicatrized fibrous tissue which is incapable of stretching during diastole. Microscopically it appears as a non-specific dense avascular hyalinized

connective tissue, except in those cases which reveal the granulation tissue of tuberculosis or pyogenic infection.

Usually both layers of the pericardium are involved; the pericardial cavity may be completely or almost completely obliterated. Occasionally there are small or large, usually sacculated collections of fluid or caseous debris, especially in the definitely tuberculous forms of chronic cardiac compression. The pericardial scar may extend over the entire cardiac surface and even over the great vessels, but it may also be localized as in one case in which there was a band of calcified scar limited only to the ventricles.[3] From the point of view of circulatory disturbance, the scar over the ventricles, especially the anterior surface, is most important because excellent results are usually obtained by pericardial resection without removal of the scar over the auricles and great vessels.

Calcification of the scar tissue, which may be observed roentgenologically, at operation, or sometimes only by microscopic examination, occurs in at least one fourth to one third of the cases.[79, 73, 35] Armstrong[1a] found calcification in 8 of 10 cases of constrictive pericarditis and only in 2 out of 28 cases of nonconstrictive adherent pericardium. In one instance there was true bone. The calcification may be so extensive as to form a hard complete shell, confining the heart (armored heart or Panzerherz).

The Heart. *The heart is usually of normal or less than normal size,* and the individual fibers may be atrophied. In 1728, Lancisi[45] had noted the characteristic syndrome of constrictive pericarditis in a young man with engorged jugular veins, enlargement of the abdomen and a small pulse, whose heart at necropsy was found to be small and surrounded by a thick, completely adherent pericardium. Chevers[16] in 1842 distinguished cases of adhesive pericarditis with enlarged hearts and valvular disease from those in which the pericardium was obliterated by a thick, almost cartilaginous deposit, the valves were normal and the heart of remarkably small size. The latter group presented the clinical picture now associated with constrictive pericarditis. Wilks[80] also called attention to such cases but the last 3 of his 6 reported cases were probably instances of rheumatic heart disease and not of constrictive pericarditis.

The heart is free from valvular lesions or any of the ordinary forms of cardiac disease. In 1 of White's[79] cases there was rheumatic cardiovalvular disease and in another congenital heart disease, both being interpreted as coincidences. Although it is possible for constrictive pericarditis and various forms of myocardial and valvular disease to be associated, it seems preferable at present to maintain strict criteria and to exclude from the former category any cases with the latter lesions. However, the superficial, subepicardial layers of the myocardium may be involved by the cicatrizing process or by tuberculous or other bacterial infection. Myocardial atrophy may be severe enough to cause functional disability.

The Liver and Other Viscera. The pathology of the organs other than the heart, in cases of constrictive pericarditis, is essentially similar to that in (right-sided) congestive heart failure.

The *liver* was long considered the site of the basic changes in the disease. Curschmann[20] noted in cases of polyserositis an inflammatory coating on the liver (perihepatitis) which he termed the Zuckergussleber (sugar-icing or frosted liver) because of the resemblance of the exudate to confectioners' sugar icing. The relation of hepatic enlargement and ascites to pericardial obliteration was noted by Rosenbach,[58] while Hutinel[39] described the occurrence of hyper-

trophic cardiac cirrhosis of the liver due to adhesive pericarditis. Pick[55] first clearly emphasized that the hepatic changes were caused by venous stasis secondary to the adherent pericardium.

As a rule the liver is enlarged in cases of constrictive pericarditis, due to venous engorgement. In later stages, the liver may become small because of atrophy and fibrous contraction. The typical nutmeg liver of cardiac failure is usually seen. Fibrosis occurs occasionally but is rarely extensive enough to cause architectural distortion. Pick[55] described the hepatic changes as a pseudocirrhosis to distinguish them from the portal cirrhosis of Laennec.

Other pathologic abnormalities may be mentioned briefly. The abdominal viscera are congested. The kidney and spleen as well as the liver may be somewhat cyanotic and firm due to congestion and fibrosis (cyanotic induration). In contrast with most cases of congestive heart failure, the lungs do not reveal significant congestion or fibrosis. But pleural adhesions and pleural effusions are usual. Large collections of ascitic fluid occur invariably with occasional secondary peritoneal inflammation and even adhesions.

Pathologic Physiology

That the constricting pericardial scar is the basic cause of the physiologic and clinical disturbances was demonstrated by (a) reproducing the clinical picture in dogs, in which Dakin's solution injected into the pericardial cavity had caused an obliterating constricting pericarditis,[29, 5] and (b) eliminating the clinical manifestations in humans with constrictive pericarditis following resection of the pericardial scar.

Diminished Diastolic Relaxation and Inflow of Blood. The constricting pericardial scar interferes with normal diastolic relaxation of the heart and thereby impairs the venous inflow into the right atrium and ventricle.[51, 16, 75] The compressing effect of the pericardial scar is best demonstrated by the striking bulging of the heart and resumption of active pulsation when the scar is excised. Systolic contraction is usually unimpaired, for the heart is capable of expelling what blood it receives although occasionally it suffers as a result of myocardial atrophy.

Diminished Cardiac Output. There is a diminished stroke output and minute volume output due to the reduction in venous inflow.[49, 13, 21, 37] The reduced cardiac output is due entirely to the diminution in output per beat since the basal cardiac rate is either normal or more often accelerated.[12] Diastolic restriction of the heart is such that the stroke output cannot be augmented during exercise; a needed increase in cardiac ouput must be effected entirely by an elevation of the cardiac rate.[14, 48]

Increased Systemic Venous Pressure and Venous Stasis. In both experimental and human constrictive pericarditis there is an early rise in venous pressure. But maintenance of an elevated venous pressure despite the diminished cardiac output depends on a greatly augmented circulating blood volume.[12] The latter, like the increased blood volume of chronic cardiac failure, is probably secondary to the deficient cardiac output and the consequent renal retention of sodium and water.

The augmented circulating blood volume and venous return cannot be accepted normally, not because of any right heart deficiency, but because of the pericardial impediment to venous inflow. The systemic venous pressure rises because of the disparity between venous return and cardiac filling capacity.

Intravenous saline infusions, given experimentally to human subjects with constrictive pericarditis,[48] do not increase the cardiac output, in contrast to their effect in acute pericardial effusion.[19] This may be due to the fact that in the former it is a nondistensible scar which prevents further ventricular filling in diastole; in the latter it is an elevated pressure which can be partially overcome.

The large circulating volume causes stasis and engorgement in the systemic venous tributaries. The circulatory disturbances resemble the inflow stasis due to tricuspid stenosis except that the impediment to right ventricular inflow is due to constriction from without. As in tricuspid stenosis also, there is no pulmonary congestion in cases of constrictive pericarditis. Despite any interference with left ventricular filling, pulmonary congestion is avoided or limited by the diminution of right ventricular output into the pulmonary circulation.

Clinical Features

The *general clinical picture* resembles that of pronounced right-sided heart failure, especially that due to tricuspid stenosis. However ascites occurs earlier and is a more prominent feature, while edema is less pronounced.

Symptoms. The *chief complaints* are most often swelling of the abdomen and dyspnea on exertion.

Abdominal swelling is due to the accumulation of ascitic fluid. It may be associated with various digestive disturbances, anorexia, abdominal fullness or even pain. Sometimes the patient's first complaint is an increase in the size of his waistline or a gain in weight despite limited food intake.

Dyspnea usually occurs only on exertion. This is presumed to be related to the inability of the heart to increase its stroke output and its limited capacity to augment its minute volume by tachycardia. However, occasionally there is dyspnea at rest, either because of extensive pleural effusions or because of the reduction in vital capacity due to marked elevation of the diaphragm by ascites. Nocturnal dyspnea and orthopnea are absent, as a rule, in contrast with congestive heart failure.

Loss of weight is common in the cases associated with active tuberculous pericarditis; but it occurs sooner or later in most cases, if allowance is made for serous effusions and edema. Weakness, fatigability, epigastric discomfort and anorexia are occasionally prominent symptoms.

Pulsations of the chest wall are minimal or absent. The heart is quiet. The apical impulse is difficult to see or feel. Broadbent's sign[11] and other signs of systolic retraction of the interspaces are absent.

Percussion of cardiac dullness reveals a small heart, or at least one without significant enlargement. There may be little or no depression of the apex on deep inspiration due to pericardiopleural adhesions. Shift of the body from right to left lateral position may be accompanied by little or no displacement of the heart.

Auscultation discloses no evidence of organic valvular disease. Systolic murmurs are occasionally heard as in many normal hearts. The heart sounds may appear distant and muffled.

The *cardiac rhythm* is usually normal. However, auricular fibrillation was noted in 4 of White's[79] 15 cases and in 2 of the 9 cases of Stewart and Heuer.[73] This arrhythmia may be due to atrial involvement by the compression scar. The cardiac rate is usually accelerated.

Examination of the lungs usually reveals signs of pleural effusions sooner or later in the course of the disease.

Signs of Circulatory Disturbance. *1. Prominent Superficial Veins.* The cervical veins are extremely engorged. There is no diastolic collapse[31] and no systolic engorgement, in contrast with cases of tricuspid valvular insufficiency. *Inspiratory swelling of the cervical veins* may be noted but this is often obscured by the constant fullness of the veins.

2. Hepatic Enlargement. Enlargement of the liver, due to venous engorgement, is often prominent and occurs early. The liver may be tender but does not pulsate (a differential diagnostic point with respect to tricuspid insufficiency). However, it may be difficult or impossible to palpate the liver if there is massive ascites. With longstanding venous stasis, atrophy and fibrosis, the liver may occasionally become small.

3. Ascites. Ascites precox. Ascites is a cardinal feature of the disease. It is characterized both by its copious quantity and its tendency to recur. However, occasionally it may not recur for months or years, even in the absence of surgical therapy. Usually the patient requires abdominal paracenteses every few weeks or months to obtain relief. In an oft-quoted classic case, 301 paracenteses were performed.

A feature of the ascites is its predominance over subcutaneous edema and especially its earlier development (ascites precox). This reverses the usual relationship of ascites and edema in cases of congestive heart failure.

The *mechanism* which accounts for the copiousness and early appearance of ascites is obscure. The older explanations implicating peritonitis,[42] pleural effusions or cirrhosis of the liver[55] as primary causes are unsatisfactory. Obviously the pericardial scar and its interference with the inflow of blood is the fundamental cause. But the consequent elevation of venous pressure in the inferior caval system should result in peripheral edema at least as early as in ascites. The possibility of greater interference with the flow of blood from the hepatic veins than from the inferior vena cava has been suggested on the basis of certain inconclusive observations.[27] The adherent pericardium on the diaphragmatic surface of the heart may obstruct lymphatic drainage of the peritoneum, which converges onto the diaphragm, and thus may increase the tendency to peritoneal effusion by further elevating the capillary pressure.

4. Subcutaneous Edema. This is often minimal or occurs relatively late. Usually, it is less prominent than the ascites. It is localized chiefly to the lower extremities or sacral region, but occasionally edema of the face, rarely of the neck, arms and chest wall, is observed when the patient arises in the morning or when he is bedridden.

5. Pleural effusions are usually present at some stage of the disease. They may be of minimal size or sufficiently copious to cause dyspnea and require thoracentesis for relief.

6. Cyanosis of slight or moderate degree is common. In view of the infrequency or mildness of pulmonary congestion, associated pleuropulmonary disease or peripheral venous stasis is probably responsible for this sign.

7. Pulsus paradoxus is almost always observed if carefully sought. Its mechanism has been discussed (p. 508).

8. Abnormal Circulatory Measurements. (a) The *venous pressure* in the antecubital veins is sharply and persistently elevated. The average values range between 25 and 35 cm., which are higher than those ordinarily seen with con-

gestive heart failure. Sodium restriction and diuresis usually have strikingly little influence on the venous pressure. Pressure over the right upper quadrant of the abdomen causes a sharp rise in venous pressure (hepatojugular reflux), even when the venous pressure is not much elevated. Exercise and intravenous infusions are more likely to elevate the venous pressure and to a greater height than in normal subjects. A fall in venous pressure often follows paracentesis. Corresponding to the rise in venous pressure, there is also an elevation of the spinal fluid pressure and of the pressure in the thoracic duct.[7]

(b) The *arterial blood pressure* is usually low. The systolic blood pressure ranges between 90 and 110 mm. Hg and rarely exceeds 120. Since the diastolic pressure is usually normal, *the pulse pressure is reduced*. This is an important sign. The pulse pressure averages between 15 and 25 mm. Hg. Corresponding to the pulsus paradoxus, the arterial pressure usually falls on inspiration.

(c) The *circulation time* may be normal or prolonged by venous stasis.[73] As in cases of congestive heart failure, the arm-to-tongue time is increased to between 20 and 40 seconds or longer. Theoretically the arm-to-lung time (ether time), should account for most or all of the delay, since the stasis occurs between the arm veins and the right side of the heart. East and Hunter[26] actually observed that the arm-to-lung time was prolonged, while the lung-to-tongue time was normal. But the observations of Stewart and Heuer[73] indicate a prolongation of circulation time through both the right heart and the pulmonary circulation.

(d) The *circulating blood volume,* as determined in 2 cases by Burwell and Blalock,[12] was increased from 30 to 45 per cent above normal.

(e) The *cardiac output* is diminished (p. 532).

(f) The *vital capacity* was reduced to between 36 and 68 per cent of normal in the cases studied by Stewart and Heuer.[73]

Hypoproteinemia. A reduction of the blood protein concentration is frequent in cases with longstanding symptoms of constrictive pericarditis. The reduction is limited to the serum albumin, the serum globulin remaining normal or even elevated. Reduction in serum albumin favors the development of both edema and ascites (p. 119).

The cause of hypoproteinemia in these cases is uncertain. It has been attributed to malnutrition (i.e., to an inadequate intake of protein), to loss of protein in the ascitic fluid which is repeatedly drained, and to a reduction in liver function due to chronic passive congestion with consequent inability to fabricate serum protein.[50] Stadler and Stinger[69] showed that hypoproteinemia persisted in a child with constrictive pericarditis even though the dietary protein intake was sufficiently high, protein nitrogen was retained, no albumin was lost and the amount of protein lost by paracentesis was far less than that administered by transfusions. Although the usual tests of hepatic function were normal, these authors concluded that the inability to regenerate serum albumin was due to liver damage caused by passive congestion. Impaired liver function as determined by the bromsulfalein test was found in all 9 cases of constrictive pericarditis reported by Harrington and Barnes.[35]

Roentgenology. Whenever possible, large pleural or peritoneal effusions which may interfere with interpretation should be removed before the heart is examined roentgenologically. The following are the most significant findings:

(1) Calcification of the pericardium[67] is the most definite evidence of an adhesive pericarditis, but does not denote constriction. The latter is usually present, however, if calcification is extensive.

(2) There is an absence or diminution of cardiac pulsation, as observed by fluoroscopy, and by roentgenkymography.[41, 72]

(3) The cardiac silhouette is usually small or of normal size. It may seem slightly or moderately enlarged, but the pronounced enlargement associated with right-sided congestive heart failure is never observed. Beck[3] has stressed the fluoroscopic appearance of a small, quiet heart as typical of constrictive pericarditis.

(4) The vascular shadow on the right, representing the superior vena cava, may be widened due to engorgement of that vessel.

(5) The absence of congestion of the lung fields may contrast strikingly with the clinical evidences of congestion of the systemic circulation. Pleural effusion and pleural thickening are common.

(6) Other roentgenologic observations are less significant. There may be any or all of the abnormalities listed above as being associated with external adhesions. These include limitation of motion of the heart with change in body position and respiration, hazy cardiac borders, tentlike shadows along the cardiac silhouette and diaphragm, abnormal or paradoxical motion of the diaphragm with respiration, and obliteration or encroachment on the retrosternal and retrocardiac spaces.

The Electrocardiogram. There is usually a low voltage of the QRS complexes. T waves are frequently flattened or inverted in lead I or II or both. Corresponding T wave alterations may be seen in chest leads. The T wave in limb leads may resemble the inverted coronary T wave of myocardial infarction. There may be slurring of the QRS complexes in all leads but no notching.[21] Fixation of the electrical axis may or may not be present.[73] Fixation of the electrical axis in cases of valvular disease with large hearts and external adhesions may be distinguished from that due to constrictive pericarditis by the high voltage of the QRS complex in the former group of cases. Auricular fibrillation has been reported in a fair percentage of cases of constrictive pericarditis.

Diagnosis

The diagnosis is usually simple if the condition is borne in mind. It is suggested by the presence of signs of congestive heart failure without signs of heart disease. Usually the diagnosis is based on the observation of venous engorgement, persistently high venous pressure, hepatic enlargement and ascites in a patient without organic valvular murmurs or other evidences of heart disease, and without cardiac enlargement. Beck[3] emphasizes the triad of chronic cardiac compression: (1) an elevated venous pressure, (2) ascites and (3) a small quiet heart. Confirmatory signs are a small and usually paradoxical pulse, low systolic blood pressure and especially a *low pulse pressure,* little or no evidence of pulmonary congestion, roentgenologic finding of diminished cardiac pulsations and occasionally of pericardial calcification, and finally little or no change in objective signs despite active treatment of congestive heart failure. A history of a pericardial rub or effusion, especially of tuberculous or other bacterial origin, may be helpful.

In a number of reported cases cardiac enlargement was said to be present.[79, 73] Occasionally elevation of the diaphragm by ascites, the presence of pleural effusions, the haziness of the cardiac borders and the width of the thick pericardium lead to an erroneous roentgenologic interpretation of cardiac enlargement. But in other instances of reported cardiac enlargement, doubt must be

raised as to whether the clinical picture is due to constrictive pericarditis or to cardiovalvular disease with coincident but clinically insignificant adhesive pericarditis. The presence of cardiac murmurs and auricular fibrillation in the cases with cardiac enlargement supports this interpretation. It is difficult to understand how, in the presence of an enlarged heart, diastolic relaxation and inflow can be seriously impaired, or how constrictive pericarditis can produce such enlargement.

Differential Diagnosis

The prominence and early development of ascites may suggest the presence of cirrhosis of the liver or of a chronic (usually) tuberculous peritonitis with or without polyserositis.

Cirrhosis of the liver may be excluded by the finding of venous congestion in the superior caval as well as in the portal system, i.e., by the observation of cervical venous congestion and elevation of the venous pressure in the upper extremities.

I have seen one case which was at first erroneously diagnosed as constrictive pericarditis because of evidences of obstruction of both the superior and inferior vena caval systems without physical signs of cardiac disease. But the correct diagnosis of *multiple venous thrombosis* (of unknown etiology) was made antemortem chiefly because of the presence of a visible collateral venous circulation on the chest wall, which does not occur in cases of constrictive pericarditis.

Primary chronic peritonitis and polyserositis are excluded by the same observations. The character of the fluid obtained by paracentesis (usually absence of bacteria or polymorphonucleosis in constrictive pericarditis) may also aid in the differentiation.

Congestive heart failure due to primary cardiovalvular or pulmonary disease is distinguished by the history and by physical, roentgenological and electrocardiographic evidence of the underlying cardiac or pulmonary disease. *Tricuspid stenosis* is distinguished by the concomitant presence of mitral stenosis and often an auricular venous pulse, while in tricuspid insufficiency there is usually a systolic hepatic pulsation and a positive cervical venous pulse.

Treatment

Once the diagnosis of constrictive pericarditis is made, the only satisfactory treatment is surgical—partial pericardiectomy (decortication of the heart).

Preoperative Management. Bed rest for a few weeks, minimal sodium intake, salt-free albumin if there is pronounced hypoproteinemia, mercurial diuretics, removal of large abdominal, pleural or pericardial effusions are the important preoperative measures (Chapter 9). Digitalis is not indicated in the classic case with normal or small heart and without myocardial or valvular disease. It may further reduce the inadequate output.[14] However, digitalization should be effected rapidly if the atrophic heart is unable to handle the increased inflow after cardiac decortication. Venesection is said to be contraindicated, for the high venous pressure serves the useful purpose of maintaining a desirable pressure head to secure an adequate inflow of blood into the heart despite pericardial compression of the heart.

Operation. If there is active pericardial infection some surgeons defer operation until the fever subsides, particularly in cases of tuberculous pericarditis. However, Blalock and Levy[8] and also Beck[4] have had successful results in some cases in which pericardiectomy had to be performed because this seemed

to be the only hope of reversing a downhill course. Blalock and Levy decided on operation for patients with active tuberculous pericarditis and cardiac compression if the patient became sicker and the venous pressure rose even though the pericardiocardiac shadow, by roentgenologic examination, was becoming smaller.

The *operative technic* has been described by various surgeons (see Schmieden;[61] Churchill;[17] Blalock and Burwell;[7] Beck;[4] Heuer and Stewart;[37] Harrington and Barnes[35]). The operation of decorticating the heart from its confining scar was first suggested by Delormé,[23] first carried out successfully by Rehn,[56] and in this country by Churchill.[17] As a rule, the scar is first dissected from the left ventricle, and when this is free to receive a greater amount of blood than previously, the right ventricle is decorticated. The pericardial scar is removed from as much of the anterior surface of the ventricles as possible without too great danger to the patient's general condition and with caution to avoid tearing the myocardium or injuring the anterior descending coronary artery. Only occasionally is it possible to resect the pericardium from the posterolateral, posterior and diaphragmatic surfaces, but this is usually unnecessary. However, Harrington and Barnes[35] emphasize the need for wide pericardial resection including the apex of the heart and diaphragmatic surface of the right ventricle. There is similar difference of opinion as to the need for removal of scar tissue from the thin-walled right atrium, which tears easily, and from the venae cavae. Harrington and Barnes believe that when the constricting pericardium is calcified, as much of the calcium as possible should be removed from the right atrium, the atrioventricular sulcus and the area around the orifices of the venae cavae. The criterion of adequate pericardial resection is the successful release of the heart and visible increase in cardiac pulsation.

To prevent the occasional occurrence of *ventricular fibrillation,* adequate aeration must be maintained, irritation of the surface of the heart by local pressure and torsion of the heart must be avoided as much as possible. Beck[4] applies 2 cc. of 5 per cent procaine to the cardiac surface when there is unusual cardiac irritability. If ventricular fibrillation occurs, Beck advises local desensitization with procaine followed by direct application to the ventricles of large electrodes and passage of an alternating current of 1 to 1.5 amperes. *Ventricular standstill* may have to be distinguished from the above by an electrocardiogram. For this reason, the electrocardiographic electrodes should be in place during the operation. Ventricular standstill is usually easy to control by cardiac massage and epinephrine.

Postoperative Management. The patient is usually placed in an oxygen tent in semi-Fowler's position and kept there for several hours or a few days. But some surgeons employ oxygen only if specially indicated. Fluids are limited. Beck[4] avoids the administration of fluids intravenously because the atrophic heart may not be able to cope with both the additional inflow of blood and the fluids. In fact venesection is sometimes indicated if there is a sharp rise in venous pressure. Digitalis or quinidine may be required postoperatively to control auricular fibrillation or other cardiac irregularities. But these are usually transient and subside spontaneously.[71]

Convalescence is usually rapid and the patient is ambulatory in four to six weeks. The restriction of sodium and the administration of diuretics should be continued until there is no longer any evidence of edema or serous effusions.

Prognosis, with and without Operation

The outlook of patients with constrictive pericarditis is almost uniformly poor if pericardiectomy is not performed. The patient is a semi- or complete invalid. Sooner or later he becomes bedridden, weak and emaciated. He suffers extremely from the recurrence of copious ascites and the need for frequent paracentesis. But to evaluate properly operative results, it must be noted that occasional unoperated patients survive for many years or decades, that sometimes without apparent cause abdominal effusions remain stationary or do not recur for years after aspiration, and finally that in occasional patients fair results may be obtained by active, prolonged, dehydration therapy.

In comparison with medical treatment, the results of pericardiectomy are brilliant when the operation is properly performed on appropriate cases. Between 50 and 75 per cent are cured or greatly improved.[4, 17, 37, 7, 54, 36, 78, 34] The mortality has ranged between 15 and 20 per cent but has diminished with increased surgical experience. The favorable effects of the operation may be noted early. During the operation, the heart should enlarge and herniate into the pericardial defect created by resection, thus indicating the removal of compression. The pulsations become noticeably greater, the pulse stronger and the systolic pressure and pulse pressure should increase. Cyanosis often disappears. The patient usually feels subjectively better when he becomes conscious and breathing is easier. The extremities feel warmer and cervical venous engorgement may be less prominent although still present. Sometimes a considerable diuresis occurs within forty-eight hours after operation; more often it is delayed.

While occasional cases show a rapid and progressive improvement immediately after operation, most successful cases require three to six months for a cure. In particular, enlargement of the liver, moderate engorgement of the cervical veins and some elevation of venous pressure may persist after other evidences of the disease have disappeared. When a successful result is obtained, not only do the serous effusions and edema disappear but the abnormal circulatory measurements are completely or almost completely restored to normal.[21, 73]

CALCIFICATION OF THE PERICARDIUM

Incidence and Etiology. Calcification occurs as a secondary degenerative change complicating chronic inflammation of the pericardium. It is observed in cases of rheumatic pericarditis,[66] pneumococcus[46] or other bacterial (purulent) pericarditis, chronic tuberculous pericarditis, traumatic pericarditis[59, 82] and in many cases of constrictive pericarditis of unknown etiology (p. 531).

Pathology. The calcium may form discontinuous plates or bands, or it may form almost a complete shell 1 to 2 cm. thick (armored heart or Panzerherz). Predominant localization is believed to occur where cardiac pulsation is least. The commonest sites of calcification are the coronary sulcus, the diaphragmatic surface of the right ventricle, the right atrium and the sternal aspect of the right ventricle, in the order named.

Calcification occurs in the parietal or epicardial layers, usually in both. As a rule there is an associated adhesive pericarditis with complete or incomplete obliteration of the pericardial cavity, or rarely a purulent pericarditis.[47] Occasionally ossification is also associated with the deposition of lime. [81, 1]

Clinical Features. Calcification of the pericardium, per se, usually causes no disturbance in cardiac physiology and no clinical subjective symptoms. However in many cases there is a clinical picture of constrictive pericarditis or of congestive heart failure due to associated cardiovalvular disease.

Roentgenology and Diagnosis. Calcification of the pericardium is recognized by roentgen ray examination[46] or is first discovered at operation or at necropsy. The first cases recognized during life were reported by Schwartz[63] and by Groedel,[33] and in this country by Case,[15] Cutler and Sosman,[22] and Youmans and Merrill.[83] A tabular review of over 70 cases was presented by Rummert.[59] Stehr[70] reported 12 of his own cases in 1938. Roentgenologic discovery is most likely if both teleoroentgenographic and fluoroscopic examinations are made.[67] A fine-grid Potter-Bucky diaphragm is helpful. Calcification is most apt to be seen in the lateral and oblique views, especially where the cardiopericardial and sternal shadows fuse. The calcium may appear as dense sickle-shaped shadows, or as massive irregular plates, streaks or branched forms. Multiple roentgenologic views are often necessary to prove the pericardial site of calcification. Pericardial calcification must be distinguished from calcification of the valves, which is centrally located in all views and shows extensive motion, from calcified thrombi, which are oval masses usually near the cardiac apex, and from calcification of the coronary arteries, of adjacent lymph nodes or of the costal cartilages.

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24

MYOCARDITIS AND MYOCARDIAL DISEASE OF OBSCURE ORIGIN

Almost every cardiac disease is associated with myocardial involvement. The most frequent and most significant types of myocardial disturbance will be presented in the individual chapters devoted to the etiologic forms of cardiac disease. This chapter is concerned with those instances of myocarditis and myocardial disease which cannot be classified etiologically as part of or secondary to some distinctive disease entity.

MYOCARDITIS

The term myocarditis was first employed by Sobernheim[46] to denote inflammation of the myocardium. Currently it refers to the myocardial lesions and symptoms associated with infectious diseases, infections and intoxications, as well as to myocardial inflammatory changes of obscure origin.[34, 24, 41, 19] It applies also to certain essentially degenerative lesions of the muscle fibers encountered in cases of diphtheria and other infectious diseases. On the other hand, myocarditis is no longer considered a proper diagnosis in cases of myocardial infarction due to coronary artery occlusion, even though an inflammatory reaction is elicited by injury of the muscle fibers. Diffuse and focal fibrosis of the myocardium, associated with hypertensive and coronary artery disease, should not be classified as chronic myocarditis or fibroid myocarditis, since the fibrous scars are due to myocardial ischemia and not to the healing of inflammatory lesions.

Myocarditis itself is rarely an adequate diagnosis, since it may be due to a variety of causes. Whenever possible, the etiologic factor should be included, such as the causative organism (e. g., meningococcus myocarditis) or chemical agent (phosphorus poisoning), or the primary disease which either produced the myocarditis (e. g., rheumatic fever) or of which the myocardial inflammation is a part (e. g., subacute bacterial endocarditis). Myocarditis is often only a pathologic-anatomic diagnosis, since the lesions may be insufficient to cause clinical symptoms or the latter may be overshadowed by other clinical features of the primary disease.

Classification. Myocarditis is sometimes classified as acute and chronic. The division is often indistinct. Myocarditis may be further subdivided into: (1) infectious and toxic myocarditis, (2) suppurative myocarditis and (3) idiopathic or isolated (Fiedler's) myocarditis. Saphir[41] classified myocarditis as

(1) myocarditis following infections with or without endocarditis; (2) specific myocarditis, e. g., rheumatic, tuberculous, etc.; (3) myocarditis due to chemical poisons, physical agents or hypersensitive states; and (4) isolated myocarditis (without associated disease).

Etiology and Incidence. The *incidence* of myocarditis is discussed with the individual causative diseases in later chapters. The available data are unreliable, first, because the pathologic diagnosis can be made only in a small percentage of cases due to the relatively low mortality in infectious diseases, and second, because these cases, being the most serious, are not representative of the disease. On the other hand, the incidence based on clinical cases is unreliable because of unsatisfactory and varied criteria employed by different observers for the diagnosis of clinical myocarditis. When routine serial electrocardiograms are made in infections, the incidence of myocarditis has been reported as being much higher than is generally supposed. But it is uncertain whether the electrocardiographic changes observed are actually due to inflammatory lesions in the myocardium. There is often a lack of correlation between pathologic changes, electrocardiographic abnormalities and cardiac symptoms or signs.

According to Saphir[41] 240 cases of myocarditis (4.3 per cent) were encountered in 5626 consecutive autopsies on adults; 186 of the cases were nonrheumatic. In a similar study among children the incidence of myocarditis was 6.8 per cent.[42] Gore and Saphir[19] reported 1402 cases of myocarditis among soldiers studied at autopsy, 90 per cent of which were rheumatic. In the majority of cases the diagnosis was not suspected clinically. These observers listed some fifty conditions associated with myocarditis, including bacterial, rickettsial, viral, fungal, protozoal and helminthic infections, glomerulonephritis, sulfonamide sensitivity, carbon monoxide poisoning, heat stroke and burns. Although they stressed the point that the clinical diagnosis could have been made frequently on the basis of symptoms and signs and electrocardiographic changes, many of the signs listed are those of shock probably due to peripheral vascular failure and not to myocarditis, while manifestations of myocardial failure are uncommon.

Rheumatic fever is the predominant cause of clinically significant myocarditis (Chapter 31). *Diphtheria* may induce a severe myocarditis (p. 834) but both the diphtheria and especially the complicating myocarditis are relatively infrequent. *Subacute bacterial endocarditis* (Chapter 34) is accompanied by a high incidence or an invariable occurrence of microscopic cardiac lesions but the clinical import of the latter remains to be assessed. The occurrence of unexpected death following an acute tonsillitis or nasopharyngitis, presumed to be due to a myocarditis demonstrated at autopsy,[5, 20] is very impressive but still remains a comparative rarity in proportion to the total number of cases of upper respiratory infections or of myocardial disease. A large number of other infections and toxic agents which are responsible for occasional instances of clinical myocarditis and for more frequent instances of histologic myocarditis are discussed in Chapter 36.

Pathology. Acute myocarditis is often subdivided pathologically into parenchymatous and interstitial forms. In the former the predominant or primary changes involve the myocardial fibers themselves; in the latter the inflammatory lesions are situated chiefly or primarily in the interstitial tissue. As a rule, however, the lesions involve both the parenchyma and interstitial tissue, and it is impossible to decide which structures were first affected.

Parenchymatous myocarditis is best exemplified by certain cases of diphtheria, but similar though less severe changes are observed in cases of typhoid fever, scarlet fever, pneumonia and other infectious diseases. The fundamental lesions are degenerative alterations of the muscle fibers. These include cloudy swelling, hyaline or vacuolar (hydropic) degeneration, granular degeneration, waxy degeneration and fatty degeneration (p. 47). The muscle fibers may be only slightly affected, or focal or large areas of muscle tissue may be destroyed and replaced by productive inflammation or fibrosis. Associated interstitial inflammatory changes appear early or late as a reaction to the muscle injury or as part of a universal myocarditis.

Interstitial myocarditis is typified by the myocardial changes in rheumatic fever (p. 706). An essentially or primarily interstitial myocarditis is observed also with meningococcic infections, trichinosis, so-called isolated (Fiedler's) myocarditis and occasionally in cases of scarlet fever, influenza and typhoid fever. The lesions are usually diffuse and consist of varying degrees of edema and infiltrations of neutrophilic or eosinophilic leukocytes, lymphocytes, mononuclear cells, occasional plasma cells and of histiocytes and fibroblasts. In rheumatic myocarditis a characteristic specific granulomatous lesion, the Aschoff body, is frequently observed. In mild forms of interstitial myocarditis, only focal lesions may occur. The muscle fibers may be normal or only little affected, but as a rule they undergo some degree of degenerative change, atrophy or necrosis.

Focal myocardial lesions, involving the parenchyma, the interstitial tissue or both, occur in various bacteremias, especially those due to pyogenic organisms or to direct extension from suppurative lesions of the pericardium or endocardium. In the latter cases and in bacteremias due to staphylococci, hemolytic streptococci and, less commonly, gonococci and pneumococci, a *suppurative myocarditis* occurs. The bacteria may produce an arteritis with swelling and necrosis of the adjacent musculature and a reactive infiltration of polymorphonuclear leukocytes. Similar foci of necrosis and leukocytes may be the result of bacterial toxins. Small or large macroscopic abscesses may result by contiguity from suppuration of the pericardium or endocardium, by septic embolization of the coronary vessels with local infarction and softening of the myocardial tissue, or by direct bacterial infection through the blood stream. Rarely, large abscesses develop and may rupture a papillary muscle, perforate the interventricular septum or heart or break into the pericardium and cause a suppurative pericarditis.

The *gross appearance* of the heart usually presents no characteristic change even though, surprisingly, diffuse and sometimes severe lesions may be discovered microscopically. Sometimes the musculature is soft and flabby and may have a dull, parboiled or glassy appearance. With suppurative myocarditis, miliary abscesses may be seen as yellow dots or streaks surrounded by a reddish zone, which yield a drop of pus when cut. Cardiac dilatation and hypertrophy may be associated with acute myocarditis, especially in cases with congestive heart failure. Endocardial (mural) thrombi are found in occasional cases of acute myocarditis.

Clinical Picture. There are often no clinical features associated with acute myocarditis as seen pathologically. Sometimes the clinical features, when present, are indistinguishable from and overshadowed by those of the primary disease or of an associated endocarditis or pericarditis, or by the manifestations

of peripheral circulatory failure. The evidences of acute myocarditis may be: (1) general symptoms, (2) cardiac signs, (3) electrocardiographic changes, (4) congestive heart failure and (5) embolism.

1. General Symptoms. These are nonspecific and include fever, leukocytosis, weakness, palpitation, precordial pain and tachycardia. They may be due to the primary disease as well as to the myocarditis. Tachycardia, out of proportion to the fever, is suggestive of myocarditis, especially in cases of rheumatic fever. On the other hand, the tachycardia may be evidence of peripheral circulatory failure due to toxemia, and especially during convalescence it may be evidence of a "labile vasomotor system" or of an "irritable heart." Bradycardia may be present with myocarditis, especially in some cases of diphtheria with heart block.

2. Cardiac Signs. A softening or diminution of the first sound has been noted as an early sign of myocarditis. The first sound may become indistinguishable from the second sound, resulting in a tic-tac rhythm (embryocardia). An apical systolic murmur occurs frequently. These are all inconclusive evidences of myocarditis, being frequently present in febrile and toxic states without myocardial lesions. A gallop rhythm is indicative of cardiac failure and, in the absence of pre-existing heart disease, suggests a myocarditis if it appears in the course of an acute infection. Under the same circumstances cardiac enlargement may indicate the presence of acute myocarditis.

3. Electrocardiographic Changes. As a result of more frequent electrocardiographic examinations of patients with infectious diseases, the incidence of myocarditis is believed to be much higher than was formerly thought. However, it is doubtful whether the electrocardiographic changes are caused by the anatomic alterations observed at autopsy. It is more probable that the former are due to electrolyte disturbances, especially in potassium, to changes in acid-base balance or to metabolic or enzymatic disturbances in the myocardium produced by the primary infection or toxic agent.

A variety of electrocardiographic changes has been described. These will be discussed more fully under the individual diseases. Most often there are elevation or depression of the RS-T interval, flattening or inversion of the T wave, prolongation of the P-R interval, or more severe grades of heart block. Sinus bradycardia occurs occasionally, while extrasystoles are common. Auricular fibrillation and flutter may occur, but usually in patients with pre-existing cardiac disease. The electrocardiographic changes are usually transient and of brief duration but not infrequently persist for several weeks after convalescence.

4. Cardiac Failure. The occurrence of acute myocarditis may be accompanied by the symptoms and signs of cardiac failure. Congestive heart failure occurs only occasionally as a result of myocarditis alone, except in rheumatic fever. On the other hand, congestive heart failure is not infrequently precipitated by an acute infection in patients with pre-existing heart disease, usually without a superimposed acute myocarditis. Thus the development of congestive heart failure during an infection suggests an acute myocarditis only if there is no associated organic heart disease.

More often, acute infections, especially when associated with severe toxemia, cause peripheral circulatory failure (shock). This may occur without any significant damage to the myocardium. Clinically the patient appears pale and faintly cyanotic and the skin has a grayish hue. The extremities and nose are cold and often clammy with perspiration. The pulse is rapid, weak and thready.

The blood pressure and usually the venous pressure also are low. The superficial veins are often collapsed. Respirations may be rapid but dyspnea is usually absent. The exact pathogenesis of this type of failure is still uncertain but except in cases of diphtheritic myocarditis it is not usually the result of acute myocarditis. Occasionally both congestive heart failure and shock are associated in the same patient. Sudden death has been repeatedly noted in cases of myocarditis complicating acute infections, often following a brief period of heart failure or shock.

5. Pulmonary or other embolism may complicate cases of myocarditis in which mural thrombosis occurs.

Prognosis. This is discussed in connection with the individual causative diseases.

Treatment. Prolongation of bed rest is indicated when myocarditis complicates an infection. Other therapeutic measures are determined by symptoms and particularly by the development of congestive heart failure.

ACUTE ISOLATED MYOCARDITIS

An acute interstitial myocarditis, of unknown etiology, characterized by a distinctive clinical and pathologic picture was described by Fiedler.[14] It is often termed Fiedler's myocarditis. Because the inflammatory lesions are limited to the myocardium, while the endocardium and pericardium are unaffected, it has also been termed acute *isolated* interstitial myocarditis.[44] Primary myocarditis denotes that it is not apparently secondary to any other known causative agent or disease. Idiopathic is another descriptive adjective applied to this disease because of the unknown etiology. The first two cases in the American literature were described by Scott and Saphir[43] and subsequent studies were reported by Simon and Wolpau,[45] Marcuse[31] and Jaffe.[23] It is doubtful whether the cases included in this category form an etiologic, pathologic or clinical entity.

Etiology. The cause of this form of acute myocarditis is unknown. According to strict criteria, no case belongs under this classification if it follows closely upon an infectious disease or if there is evidence of hypertension, coronary disease, previous rheumatic fever or any other known cause of heart disease. Most cases occur in the third decade, but some have been reported at diverse age levels from childhood to old age. A predominance of males has been noted.[31]

A variety of causative agents or mechanisms have been postulated to account for these cases of idiopathic myocarditis, including a virus[7] and unknown bacterial toxins. Recent pathologic and experimental observations have suggested that the myocarditis may represent an allergic reaction, particularly hypersensitivity to the sulfonamide drugs. Myocarditis has been reported due to the administration of serum[6, 33] and to arsphenamine sensitivity.[4] French and Weller[17] reported histologically proven interstitial myocarditis in 55 per cent of 227 patients given sulfonamides in their final illness. The lesions were characterized by eosinophilic cellular infiltrations and by the occurrence of large mononuclear cells of the clasmatocyte type. Similar lesions were produced in the experimental animal by the administration of sulfonamides. However, in a recent study of the problem Fawcett[13] observed no difference in the incidence of interstitial myocarditis before or after the advent of sulfonamide drugs. Nor did he find any evidence that the administration of these compounds shortly

before a patient's death was associated with either an increase in the total number of myocardial interstitial cells or an excess of a particular type of cell.

Pathology. The heart is usually dilated and hypertrophied, often strikingly so. Heart weights between 500 and 700 gm. are not uncommon, but the heart may be of normal size.[21] The heart muscle often appears pale and is studded with irregular, yellowish or gray streaks or dots. It may be soft and friable. The pericardium and endocardium are not involved, but intramural thrombi are frequently encountered. The coronary arteries are normal.

Microscopically, there is a widespread infiltration of cells in the interstitial tissue. The nature of the cells differs somewhat in the various cases, but they are usually neutrophilic or eosinophilic leukocytes or lymphocytes. Endothelial cells, plasma cells and fibroblasts are also observed, and may predominate. There may be evidence of granulation tissue and early reparative changes. The muscle fibers may disclose edema and degenerative alterations but these are relatively slight. Although the interstitial changes are far more prominent, they may represent a reaction to metabolic, allergic or toxic disturbances in the muscle fibers.

Clinical Features. Often there are no significant symptoms and the diagnosis is made on histologic examination.[31] When cardiac symptoms are manifested, the characteristic clinical picture is one of rapidly progressive congestive heart failure. The onset may be gradual or acute. As a rule, in the beginning, fever is absent or only slight. The remainder of the course is one of low fever alternating with afebrile periods. Moderate or high fever may occur toward the end of the disease, less commonly at the outset. Rarely there is a septic febrile course resembling that of bacterial endocarditis. Blood cultures are negative. In a few cases the onset and course resemble those of myocardial infarction,[2, 21] but there is some doubt in at least some of these cases whether they properly belong to the group under discussion.

The outstanding symptoms are dyspnea and weakness. Mild precordial oppression and palpitation are not uncommon. The patient is often apprehensive. There may be a grayish cyanosis of the skin. Eventually there are classic signs of congestive heart failure, including enlargement of the liver, peripheral subcutaneous edema, congestion of the superficial veins and occasionally effusions in the serous cavities. The clinical picture may begin with or be complicated by embolization of the pulmonary or cerebral vessels. Hemiplegia and cough with bloody expectoration have been observed.[8] Emboli probably arise in the intramural cardiac thrombi mentioned above. Infarcts of the kidney and lungs have been found at postmortem examination.

The *heart* is usually enlarged, often considerably so. The heart sounds may be muffled and there may be an apical systolic murmur. Freundlich[18] found the circulation time considerably prolonged and the venous pressure extremely elevated. Extrasystoles are not uncommon and auricular fibrillation has been reported.

The electrocardiogram may reveal no significant abnormalities. Occasionally, as first noted by de la Chapelle and Graef,[8] conduction defects may be disclosed by a prolonged P-R interval and intraventricular block.

The leukocyte count is often normal, especially in the cases with little or no fever, but leukocytosis is not uncommon at some stage of the disease.

Course and Prognosis. The course is unfavorable; cardiac failure is progressively more severe and almost always there is a fatal outcome within two

weeks. Occasionally the duration is measured in months. In the cases of isolated myocarditis studied by Jaffe[23] in Venezuela, the heart failure followed a chronic course lasting months or years. Idiopathic isolated myocarditis with progressive fatal course but of subacute or chronic duration has also been reported by Boikan[3] and by Franz.[16] About 15 per cent of the patients die suddenly,[22] the clinical picture being that of acute cardiac failure with pulmonary edema. When an occasional patient is said to have survived, there is always uncertainty as to the diagnosis, since definite proof of the diagnosis requires pathologic examination.

Diagnosis. The clinical diagnosis should be suspected when congestive heart failure occurs in a person without evidence of congenital, valvular, hypertensive or arteriosclerotic heart disease, and without a history of rheumatic fever or a preceding infection, in whom no other known cause of cardiac disease can be discovered. A rapidly fatal course is confirmatory evidence.

The *treatment* is that of congestive heart failure and is symptomatic.

IDIOPATHIC HYPERTROPHY OF THE HEART

A variety of cases of cardiac hypertrophy of obscure origin have been classified under the heading of idiopathic cardiac hypertrophy. As our knowledge has increased, cases of so-called idiopathic cardiac hypertrophy have been separated from this category and assigned to definite causes such as hypertension, congenital lesions and von Gierke's disease (p. 959). Chronic severe anemia, beriberi, pulmonary lesions and congenital anomalies of the coronary arteries are among other causes of cardiac hypertrophy which have sometimes been overlooked in the past.

"Congenital" Idiopathic Hypertrophy. In the majority of reported cases of cardiac hypertrophy of obscure origin, the patients have been infants or children. Hence many of them have been classified as congenital idiopathic cardiac hypertrophy, 70 examples of which were collected from the literature by Weisman[48] in 1942. In addition to dilatation and hypertrophy these hearts often present endocardial or perivascular myocardial fibrosis.[30] Kugel and Stoloff,[26] in a review of cases of idiopathic cardiac hypertrophy in infants and young children, concluded that careful histologic study usually excluded a "congenital" origin for the hypertrophy. In their own cases there was usually degeneration and fibrosis of the heart muscle fibers or inflammatory foci (lymphocytic), which they suggested might be the result of infection in utero or in the early days of life.

In these cases, there are no cardiac murmurs and the course is usually afebrile. Distress at feeding, dyspnea, cyanosis and tachycardia may be prominent features. There is an abrupt onset of heart failure with rapid progression often terminating in sudden death.[25] The electrocardiogram may reveal low voltage of the QRS complexes, shallow T waves or a prolongation of the P-R interval.

Cardiac Hypertrophy in Young Adults. Levy and von Glahn[27] reported 10 instances in young adults of cardiac hypertrophy of unknown etiology. In all there were symptoms of cardiac failure. The heart sounds were weak and gallop rhythm was frequently present. There were no murmurs of valvular disease. In some there was electrocardiographic evidence of myocardial damage and arrhythmias. Infarction of the lungs, kidneys or spleen was frequent. Death was due to progressive or recurrent cardiac failure in 7 patients and

occurred suddenly in 3. At necropsy there was striking cardiac hypertrophy, the average heart weight being 563 gm. There was no significant coronary artery disease or arteriolar sclerosis. In 4 cases microscopic examination of the heart revealed only hypertrophy, in 2 a slight increase in connective tissue, but in the remaining 4 there was extensive scarring with or without recent necrosis. There were mural thrombi in six of the hearts. In the cases of Flynn and Mann[15] which were characterized by endocardial and subendocardial degeneration, mural thrombi and heart failure were associated with well known etiologic causes of heart disease. In 2 cases of cardiac hypertrophy of obscure cause, reported by Ware and Chapman,[47] there was a chronic fibroplastic myocarditis characterized by extensive replacement of myocardial fibers by fibrous tissue. Norris and Pote[36] reported 4 fatal cases of heart failure associated with unexplained hypertrophy of the heart in young men. Evans[12a] described a familial type of cardiomegaly in young adults not unlike the cases described by Levy and von Glahn.

Right Cardiac Hypertrophy and Endocardial Thrombosis of Obscure Origin. Recent interest has been attracted to cases of idiopathic hypertrophy confined to or affecting predominantly the right cardiac chambers. All known causes of right cardiac hypertrophy had been excluded in these cases by both clinical and microscopic examination. Reports of cases of idiopathic hypertrophy of the right heart have been made by Oppenheimer,[37] de Navasquez et al.,[9] East,[10] Armstrong[1] and Rosenbaum[40] among others. The patients were predominantly females of all ages. There was a history of progressive dyspnea later associated with cough, cyanosis and advanced right-sided heart failure. In some cases there was a systolic pulsation and a systolic murmur over the pulmonic area and an accentuated second pulmonic sound. *Roentgenologic examination* disclosed dilatation of the pulmonary arteries and right ventricular enlargement. The *electrocardiogram* disclosed evidence of right ventricular strain and, in some instances, right atrial enlargement and right bundle branch block. In almost all cases death occurred from congestive heart failure. At autopsy there was predominant or isolated hypertrophy of the right atrium, right ventricle or both, and pronounced dilatation of the pulmonary artery and its branches.

SCLERODERMA

Scleroderma, generally known as a cutaneous disease associated with local or diffuse thickening and induration of the skin, and sometimes of skeletal muscle, also affects a variety of internal organs including the lungs, the esophagus and the heart. Weiss and his associates[49] first emphasized the cardiac lesions and employed the term scleroderma heart disease. Weiss et al.[49] and Mathisen and Palmer[32] described multiple focal areas of thickened collagen fibers extending from endocardium to pericardium. Myocardial disturbance results from encroachment on and destruction of the muscle fibers.[11] The coronary arteries are patent.

Clinical evidence of cardiac involvement appears long after the cutaneous disturbances but occasionally cardiac symptoms precede those referable to the skin. Palpitation and dyspnea on exertion are early symptoms and may be followed by frank and progressive manifestations of congestive heart failure. Gallop rhythm, prolongation of circulation time and elevated venous pressure have been noted. Heart block may occur.[11] Roentgenologic examination may disclose enlargement of the heart with shadows at the bases of both lungs.

The electrocardiogram, in the case reported by Mathisen and Palmer,[32] showed a prolongation of the P-R interval, slurred QRS complexes of low voltage, diphasic T waves and depressed ST segment in lead I.

MYOTONIA ATROPHICA

This is a familial disease characterized by increased muscle tone, atrophy of muscles (face, neck, thigh, forearm, hand), dimpling of tongue when the lower teeth are struck by a hammer, cataract formation, premature baldness, testicular atrophy and impotence. It may represent a later stage of myotonia congenita of Oppenheim.[28]

Maas and Zondek[29] first called attention to cardiac involvement in this disease. Mondon and Pasquet[35] and Romano and Michael[39] emphasized the frequency of cardiovascular abnormalities, especially coronary arteriosclerosis. Recently Evans[12] described the cardiac findings in 13 cases of myotonia atrophica. The electrocardiogram disclosed a prolonged P-R interval, low voltage of the P waves, slurring of the QRS, left axis deviation and bundle branch block. In two cases there were breathlessness and cardiac enlargement but no other signs of heart failure. The first sound at the apex may be split. In other cases bradycardia, hypotension, depression of ST segments and inversion of T waves with little or no cardiac enlargement have been noted.[38] There may be a triple rhythm. Quinine may afford some relief to the myotonia, but does not alter the progress of the disease.

FRIEDREICH'S ATAXIA

Attention has been called in the French and British literature to the finding of cardiac lesions and electrocardiographic changes in individuals suffering from Friedreich's hereditary ataxia. Russell[40a] described pronounced cardiac hypertrophy, fatty and eosinophilic degeneration, and lymphocytic interstitial myocarditis in children and young adults with Friedreich's disease, some of whom died of heart failure. Evans and Wright[12b] observed complete heart block and bundle branch block, or RS-T and T wave changes resembling those seen in cases of myocardial infarction.

PROGRESSIVE MUSCULAR DYSTROPHY

Myocardial fibrosis and mild degenerative and inflammatory changes, somewhat similar to those in the skeletal muscle, have been observed in the hearts of individuals with progressive muscular dystrophy.[18a, 2a] In occasional cases, tachycardia, arrhythmia or heart failure had been present.

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ENDOCARDITIS AND ENDOCARDIAL DISEASE

DEFINITION

Endocarditis in its narrowest sense refers to exudative and proliferative inflammatory alterations of the inner lining of the heart. The term was first introduced by Bouillaud.[6] Sometimes the term endocarditis is applied rather loosely to a number of simple thrombotic or degenerative lesions of the endocardium. Endocarditis most frequently involves the valvular endocardium, but it may also affect the inner lining of the cardiac chambers (parietal or mural endocarditis) or the endocardium of the chordae tendineae, papillary muscles or trabeculae carneae

CLASSIFICATION

Endocarditis is merely a general pathologic-anatomic diagnosis which does not reveal the different etiologic factors concerned. A complete diagnosis should also include the causative bacterial agent or the general disease of which the endocarditis is a part. According to the studies of Libman[27] as well as my own observations with Gross, endocarditis may be classified as:

1. Acute and subacute bacterial endocarditis.
2. Rheumatic endocarditis.
3. Atypical verrucous endocarditis of Libman-Sacks disease.
4. Nonbacterial thrombotic endocarditis (terminal or cachectic endocarditis, thromboendocarditis or nonbacterial thrombosis of the endocardium).
5. Syphilitic endocarditis.
6. Tuberculous endocarditis.
7. Unclassified.

In addition there are a number of degenerative alterations of the endocardium which may be primary, or superimposed on a preexisting endocarditis. These degenerative changes include endocardial sclerosis, calcification, or rarely ossification, fatty degeneration, mucoid softening and amyloidosis.

Endocarditis may be one element of a more extensive cardiac disease in which the myocardium, pericardium or both are simultaneously involved. Sometimes the endocarditis is only one feature of a generalized disease in which it may be the primary factor determining the clinical picture or merely a secondary element with or without significant clinical manifestations. For these

reasons the main forms of endocarditis, such as the bacterial and rheumatic, are discussed separately and in detail in connection with etiologic diseases of which they are a part. Syphilitic and tuberculous endocarditis are rare and unimportant and are considered briefly in connection with other syphilitic and tuberculous lesions of the heart. The purpose of this chapter is to provide an orientation to the different forms of endocarditis.

It is important to distinguish endocarditis itself from the end results or complications of endocarditis. The latter include valvular defects and emboli. Valvular defects arise because of the thickening, shortening and deformity of the cusps and chordae tendineae resulting from organization, fibrosis, contraction and adhesions, which represent healing of the inflammatory process. These, by preventing proper apposition, opening and closing of the valve cusps, produce valvular stenosis or insufficiency. Emboli result from the detachment of particles of friable verrucae (usually containing bacteria) or of parietal endocardial thrombi, which may develop at the site of parietal endocarditis. The formation of auricular or ventricular mural thrombi is facilitated by the presence of endocarditis at the sites involved.

GENERAL PATHOLOGY OF ENDOCARDITIS

The pathology of endocarditis is characterized by the presence of verrucae on the surface of the endocardium and by changes in the endocardium itself.

1. Verrucae. Superficial excrescences or vegetations termed *verrucae* (Laennec), situated usually on the surface of the valvular endocardium but occasionally also on the parietal endocardium, constitute the most obvious feature of endocarditis. It is not always possible to determine the nature of the endocarditis by examination of the verrucae alone, but not infrequently such a diagnosis can be made with reasonable accuracy by a combined consideration of the size, location and appearance of the verrucae and of the bacteriological examination. The examination of slides containing stained crushings of the verrucae divides the endocarditides into two major groups, the bacterial and the nonbacterial. The vegetations of bacterial endocarditis reveal *numerous* organisms in such spreads, except in the bacteria-free stage of subacute bacterial endocarditis (p. 796). Cultures from the vegetations may help to identify the causative organism, but postmortem cultures are not always reliable.[10] Identification of the causative organism usually enables a differentiation between acute and subacute bacterial endocarditis. Final diagnosis requires a consideration also of the antemortem bacteriology (blood cultures) and the clinical course. If there are no bacteria in the vegetations, they are due to rheumatic endocarditis, healed bacterial endocarditis, atypical verrucous endocarditis (Libman-Sacks disease) or nonbacterial thrombotic endocarditis.

The *size of the vegetation* is not a reliable means of differentiating the various forms of endocarditis. Minute yellowish soft vegetations about 0.5 to 2 mm. in diameter, situated in beadlike fashion along the closure line of the cusps, are usually rheumatic. But terminal acute bacterial endocarditis or terminal nonbacterial thrombotic endocarditis may produce vegetations of similar size and location. Usually the bacterial vegetations are larger than the rheumatic, averaging about 5 mm. in size. When multiple, they may be as small as 1 or 2 mm. while occasionally there are isolated vegetations, 1 to 2 cm. in diameter or even larger. The nonbacterial thrombotic verrucae may be as small as the usual rheumatic vegetation or may form larger conglomerate masses or stalked

polyps. The huge irregular, ulcerated or purulent cauliflower vegetations which are occasionally observed generally represent acute bacterial endocarditis. Sometimes the bacterial vegetations are greatly enlarged by the accretion of currant jelly clot to their ulcerated surface. When situated on the mitral valvular endocardium, they may enhance or produce a mitral stenosis, or act as a ball-valve thrombus to occlude completely the mitral orifice. The vegetations in atypical verrucous endocarditis may be indistinguishable in size from rheumatic verrucae, they may form massive conglomerate lesions, or they may be of the flat spreading variety which covers a considerable portion of the valvular surface.

The *location and distribution* of the vegetations may be diagnostically suggestive. Definite elevated verrucae on the posterior wall of the left ventricle are usually bacterial, mostly of the subacute variety. The presence of mural endocardial lesions (except minute ones in the left atrium) practically excludes a rheumatic etiology and suggests bacterial endocarditis or atypical verrucous endocarditis. Verrucae situated exclusively or chiefly on the tricuspid leaflets without simultaneous lesions on the aortic leaflet usually represent atypical verrucous or bacterial endocarditis. Verrucae which are situated only or predominantly in the pockets of the atrioventricular valves and the adjacent ventricular myocardium are almost always due to atypical verrucous endocarditis. Vegetations which are associated with ulceration and aneurysm of the cusps and rupture of the chordae tendineae are bacterial in origin. If there is complete perforation of a cusp, it is due more likely to acute than to subacute bacterial endocarditis. The nonbacterial thrombotic vegetations, like the rheumatic, are limited essentially to the atrial surface of the atrioventricular cusps and to the ventricular surface of the semilunar cusps; they affect the mitral, aortic, tricuspid and pulmonic valves in that order of frequency, individually or in combination.

Bacterial vegetations may occur simultaneously with nonbacterial vegetations in the same heart and even on the same cusps. Thus subacute bacterial endocarditis is frequently superimposed on an active rheumatic endocarditis, and an acute terminal bacterial endocarditis is a common complication of the atypical verrucous endocarditis of Libman-Sacks disease.

Microscopically, the superficial part of the vegetation consists of a cap of thrombotic material composed of agglutinated blood platelets surrounded and permeated by fibrin, leukocytes and scanty erythrocytes. Beneath the thrombus cap, which may be very tiny or quite large, is a variable amount of proliferated or degenerated valve substance. Beneath this there is an inflammatory reaction or fibroblastic proliferation and fibrosis. In the bacterial forms the entire verrucae from surface to base may contain diffuse masses or isolated packets of bacteria. In the rheumatic and subacute bacterial endocarditides, the base of the verrucae shows a considerable amount of organization. In the rheumatic and healed forms of subacute bacterial endocarditis, the major part of the verrucae may be converted into fibrous tissue and may be hyalinized. In such instances the surface of the verrucae may be covered with endothelium which has grown in from the sides. The whole vegetation may be converted into a fibrous nodule with varying amounts of lime and extremely rarely with bone.

The above elements are present to a varying degree in the different forms of endocarditis. In the nonbacterial thrombotic forms, the blood-platelet thrombus may form the entire or major element with little or no subjacent degener-

ated (fibrinoid) valve tissue and with little or no inflammatory reaction. In the bacterial forms, masses of bacteria, leukocytes, fibrin and platelets are the essential components. Rheumatic verrucae are composed predominantly of inflamed, proliferating and degenerated valve substance with a small cap of blood-platelet thrombus. In atypical verrucous endocarditis the verrucae often spread over a wide area on both surfaces of the cusp and consist essentially of desquamating, swollen and degenerated superficial endothelial and subendothelial cells.

2. Changes in the Endocardial Substance. The inflammatory changes in the endocardium itself are often the essential feature of endocarditis, although their macroscopic appearance is less striking than that of the verrucae. Valvular endocarditis, especially in rheumatic fever, but occasionally also in Libman-Sacks disease, may occur without the formation of verrucae. Even when verrucae are present on one or more of the valves, a valvulitis without verrucae may be found on the others. An auricular endocarditis is almost always found in association with acute rheumatic heart disease, but overlying verrucae are usually absent or barely visible.

The most intense inflammatory reaction is found in rheumatic endocarditis (see below). Beginning in the ring of the cusp, it extends a short way or more often to the closure line or tip. The inflammatory reaction is both proliferative and exudative, the valve is vascularized and organization occurs early. Necrosis is absent. On the other hand, in the acute bacterial endocarditis, valvular necrosis is a prominent feature, while inflammatory reaction is scant except for polymorphonuclear leukocytes within the vegetation and in the immediate vicinity of necrotic areas. Subacute bacterial endocarditis produces a lesser degree of necrosis and a greater degree of inflammatory reaction, the latter being characterized by the infiltration and proliferation of mononuclear cells. The valves in atypical verrucous endocarditis may or may not suffer some necrosis. An inflammatory reaction tends to be located near both surfaces of the cusps and near the pocket of the valve. Plasma cells, large mononuclear cells and endothelial bud capillaries are prominent features. In nonbacterial thrombotic endocarditis the cusps are strikingly free from acute inflammatory change, but in most instances they are thickened and deformed by considerable fibrous tissue representing chronic healed rheumatic endocarditis.

General Pathogenesis of Endocarditis. The etiology and pathogenesis of endocarditis are discussed in connection with the individual forms of endocarditis.

CHARACTERIZATION OF INDIVIDUAL FORMS OF ENDOCARDITIS

Acute Bacterial Endocarditis (p. 806).
Subacute Bacterial Endocarditis (p. 774).
Rheumatic Endocarditis (Chapters 31–33).

Atypical Verrucous Endocarditis (Libman-Sacks Disease) (Acute Diffuse Lupus Erythematosus)

This is a form of endocarditis with nonbacterial verrucae which are usually macroscopically different from rheumatic verrucae and which were first observed in 4 cases of a fatal febrile disease reported by Libman and Sacks.[28] The latter is a clinical-pathologic entity which includes the cases of acute disseminated lupus erythematosus with constitutional symptoms.[22] The endo-

cardial verrucae are frequently absent and are not significant for the clinical picture.[18, 12] Endocardial lesions were found by Humphreys[21] in 12 of 21 cases of acute disseminated lupus erythematosus. Like rheumatic endocarditis, atypical verrucous endocarditis is only one part of a general febrile disease, in which blood cultures are negative and in which serous membranes, the skin, the blood vessels and other structures may be affected. But unlike rheumatic fever the cardiac lesions, including the endocarditis, are clinically unimportant.

Etiology. The cause of the disease is unknown. A remarkable feature is its occurrence almost exclusively in young women of childbearing age. A tuberculous etiology is no longer tenable.[23] A streptococcal origin has been maintained by Barber[4] but without direct evidence. Like periarteritis nodosa and rheumatic fever, Libman-Sacks disease has been interpreted as an allergic (hypersensitive) tissue reaction, chiefly on the basis of the pathologic findings.[31, 11, 35, 32] However there is no definite clinical evidence to support this interpretation[3] although several cases have appeared among student nurses following the injection of Dick toxin.[1] A relationship to an anterior pituitary or adrenal cortical disturbance is being investigated.

Endocardial Lesions. The verrucae are usually broader and more massive than in rheumatic endocarditis and have a great tendency to involve the mural endocardium, the endocardium of the valve pockets, both sides of the cusps, and the right side of the heart.[18] The tricuspid valve is more often affected than the mitral, and the pulmonic more often than the aortic. The verrucae consist of areas of proliferating and degenerated valve substance mixed with fibrin and platelet thrombi. The cusps contain large mononuclear and plasma cells, macrophages, fibroblasts, capillaries of the endothelial bud type and necrotic cells forming characteristic hematoxylin-stained bodies.[18] Not uncommonly there is a terminal bacterial invasion of the blood stream with the production of an acute bacterial endocarditis. A nonbacterial terminal thrombotic endocarditis (see below) may also be associated with atypical verrucous endocarditis or it may occur as the only macroscopic endocardial lesion in Libman-Sacks disease. Although there is no evidence that the atypical verrucous endocarditis itself produces clinical symptoms or valvular deformities, there are distinctive clinical features associated with the general disease.

Myocardial Lesions. In the myocardium the lesions vary from minimal thickening of collagen, foci of round cells, atrophy of fat or interstitial edema to pronounced increase in density of intermuscular collagen, fibrinoid necrosis of collagen and vessel walls, thickening and stenosis of small arteries and fine scars suggestive of small infarcts. Aschoff bodies are absent. The heart is usually of normal size but may be slightly hypertrophied.

Pericardial Lesions. Adhesive pericarditis is frequent and a serofibrinous pericarditis is not uncommon. In 5 of the 21 cases analyzed by Humphreys[21] there were effusions of 600 to 950 cc.

The changes in the heart appear to be part of a widespread alteration of the collagen tissue[25, 24] with involvement of endothelial-lined structures.[2] The serous membranes, vasculature (especially the glomerular capillaries), lymph nodes,[16] skin, and mediastinal and retroperitoneal areas are affected. Fibrinoid metamorphosis and fragmentation of collagen, swelling and increased density of the interfibrillar ground substance, wire-loop lesions and focal necrosis of the glomerular capillaries, sclerosis of the collagen fibers around the follicular arteries of the spleen and the endocardial lesions are the most conspicuous

diagnostic features. Although similarities to periarteritis nodosa, rheumatic fever and scleroderma have been stressed, the pathologic and clinical features of each are usually easily distinguishable. Some confusion has arisen because Libman-Sacks disease may be associated with necrotizing arteritis or occasionally with scleroderma.

Clinical Features. Although Libman-Sacks disease is not a clinical cardiac ailment, its chief clinical features merit brief discussion because it is often confused with rheumatic fever or bacterial endocarditis.

Fever is an essential feature. The onset is usually characterized by diffuse arthralgias and stiffness of the small and large joints of the extremities. Occasionally there are joint changes resembling those of rheumatoid arthritis. Not infrequently the patient is first treated for arthritis, for which he goes to the seashore, where exposure to the sun is followed by distinctive cutaneous lesions.

The acute disseminated lesions of lupus erythematosus are most often suggestive of the diagnosis but these lesions may be absent or develop late in the disease. The lesions consist of a characteristic, slightly raised erythematous butterfly eruption across the bridge of the nose and extending to the cheeks. Papular and erythematous lesions of a bluish-red cast also affect other parts of the face, the forehead, the ears, the manubrium sterni, the volar surface of the fingers, the thenar and hypothenar eminences and other parts of the upper and lower extremities. Telangiectatic and petechial lesions also occur. The skin of the face may become scaly and edematous, and the lesion may resemble that of seborrheic dermatitis or erysipelas. Erythematous or ulcerative lesions may appear on the hard palate or other parts of the oral mucosa.

Albuminuria, microscopic hematuria or the presence of clumped leukocytes in the urine often appears early and may suggest a diagnosis of glomerulonephritis or pyelonephritis. The fundi may disclose cotton-wool exudates and hemorrhages due to local vascular lesions (angiospasm, segmentation of arterioles), while the blood pressure is almost always normal. Fleeting or persistent pleuropneumonic lesions, pleurisy with effusion which may be eosinophilic, or evidence of serofibrinous pericarditis are commonly observed. Lymphadenopathy and splenomegaly, Raynaud-like phenomena, scleroderma and cerebral manifestations occur occasionally and evidence of impaired renal function, bronchopneumonia and bacterial endocarditis appear late in the disease or preterminally.

Leukopenia, anemia, occasional thrombocytopenia, a reduction in plasma albumin, hyperglobulinemia and an occasional false positive Wassermann test are additional features.

The electrocardiogram discloses no characteristic changes but occasionally there may be low voltage of the QRS complexes, an increased P-R interval, low or inverted T waves, and a tendency to a prolonged Q-T interval.[29]

Diagnosis. Most often Libman-Sacks disease is confused with rheumatic fever, rheumatoid arthritis or subacute bacterial endocarditis, but also with glomerulonephritis or pyelonephritis, pleuropericarditis or rarely Hodgkin's disease if there is a prominent lymphadenopathy.

The combination of fever, arthralgia, lupus erythematosus and leukopenia in a young woman is usually adequate for diagnosis. The blood culture should be negative except in the terminal stage. Rheumatic fever and periarteritis nodosa are associated with a polynuclear leukocytosis, as a rule.

In the absence of characteristic cutaneous lesions, Libman-Sacks disease may be suspected in cases resembling rheumatic fever in which there is evidence of acute glomerulonephritis and azotemia, but with a normal blood pressure. Similarly the association of thrompocytopenic purpura or of leukopenia or both in cases resembling rheumatic fever should suggest Libman-Sacks disease. The combination of azotemia, fever and normal blood pressure may also be due to this disease. It has also masqueraded as a subacute polyserositis with fever, with or without "arthritis" and "glomerulonephritis."[36, 7] In cases resembling bacterial endocarditis, but in which the blood cultures are persistently negative, Libman-Sacks disease should be suspected, especially if there is no organic cardiac murmur.

Treatment is unsatisfactory although there are occasional transient remissions. The administration of testosterone, sterilization doses of roentgen ray therapy over the ovaries and oophorectomy have been tried. Darkening of the room and avoidance of exposure to sunlight appear desirable. Vitamin therapy has been administered empirically. Thoracentesis is occasionally required if there are respiratory symptoms due to large pleural effusions. Salicylates may ameliorate the joint pains and fevers. Transfusions are indicated if there is pronounced anemia and hypoproteinemia. Penicillin or streptomycin may be required to control complicating infections. Death usually occurs within a period of six months to two years, but I have seen some patients who have thus far survived four years or longer. At present pituitary adrenocorticotropic hormone and compound E of the adrenal cortex are being given a therapeutic trial in this disease.

Nonbacterial Thrombotic Endocarditis

This refers to the verrucous endocardial lesions which are associated with a variety of infections and chronic wasting diseases. The term cachectic endocarditis was applied by Harbitz[20] to these lesions but because they occur toward the end of the disease, they have also been classified as terminal endocarditis. Many of the lesions diagnosed as terminal endocarditis prove on careful bacteriologic and microscopic examination to be examples of active rheumatic verrucous endocarditis or terminal bacterial endocarditis.[19] The latter two forms should be distinguished from the cases under consideration. The term thromboendocarditis was introduced by Ziegler[37] to emphasize the essential thrombotic nature of the lesions. Königer[26] in his extensive study of endocarditis referred to this group as simple thromboendocarditis. It is preferable to avoid this term, which according to recent usage has come to be applied to all types of nonbacterial verrucous endocarditis, including rheumatic endocarditis. Gross and Friedberg[19] introduced the term nonbacterial thrombotic endocarditis to denote the essential descriptive features. But it is questionable whether the term endocarditis may be properly employed in these cases since there is little or no inflammatory reaction in the cusps. Perhaps nonbacterial thrombosis of the endocardium would be a more accurate term although it is probable that the deposition of thrombus is secondary to a toxic damage to the cusp itself.[26, 8]

The essential feature in these cases is the presence of nonspecific valvular vegetations which may resemble those of rheumatic endocarditis. Sometimes they are minute and arranged in rows on the closure line of the cusps. But they may be much larger than rheumatic verrucae and appear as a pyramidal ridge or a massive solitary sessile or pedunculated lesion. The mitral, aortic and tri-

cuspid valves are affected in that order as in rheumatic endocarditis. Neither the mural endocardium nor the chordae are involved. Valvular deformities do not result from the lesions.

Microscopically the vegetations consist essentially of agglutinated blood-platelet thrombi. Superficially there is a small or large cap of fresh thrombus often overlying an amorphous irregular area of valve substance which has undergone eosinophilic or fibrinoid degeneration. There are no bacteria in the vegetation. A striking feature, which contrasts with the findings in active rheumatic endocarditis, is the absence or paucity of inflammatory reaction in the cusp, despite the freshness of the verrucous lesion. When cells are present, they are usually fibroblasts and histiocytes which participate in early organization of the base of the verrucae. There are no Aschoff bodies in the heart. In a preponderant majority of cases, the verrucous lesions are superimposed on thickened, fibrotic deformed valves, usually the result of chronic rheumatic endocarditis.

Nonbacterial endocarditis is an accidental occurrence in a variety of infections and chronic wasting diseases which, as far as we know, has no clinical significance, except that it may facilitate a superimposed bacterial endocarditis. The nonbacterial verrucous lesions appear most often in association with carcinomatosis, glomerulonephritis, chronic pulmonary disease including tuberculosis, uremia, lobar pneumonia, leukemia, osteomyelitis, cirrhosis of the liver and Libman-Sacks disease. The possibility that metabolic or bacterial toxins may contribute to valvular injury and subsequent endocardial thrombosis has been mentioned. Previous valvular deformity by rheumatic endocarditis favors secondary deposition of nonbacterial thrombi. Friedberg and Gross[13] observed 3 cases of nonbacterial thrombotic endocarditis associated with fever, essential (thrombocytopenic) purpura hemorrhagica, and vascular lesions. The endocarditis was not related to the clinical picture. Friedberg, Gross and Wallach[14] also reported 4 cases of this form of endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and vascular lesions. The latter may now be classified as examples of Libman-Sacks disease. The nonspecific nonbacterial thrombotic endocarditis as well as the characteristic atypical verrucous endocarditis (and a terminal bacterial endocarditis) may occur in Libman-Sacks disease.

Syphilitic Endocarditis

This is rarely if ever a primary endocarditis, but results from the contiguous spread of the syphilitic aortic lesion to the commissures and bases of the aortic cusps (p. 819). Rarely the aortic leaflet of the mitral valve is involved by contiguous spread of syphilitic inflammation from the aorta.[33]

Tuberculous Endocarditis

This occurs very rarely. The endocardium may be involved by extension of a tuberculous perimyocarditis or by miliary tubercles in instances of generalized miliary tuberculosis (p. 843).

Loeffler's Fibroplastic Endocarditis Unclassified

Certain inflammatory lesions of the endocardium still cannot be accurately classified. Among these are the cases of isolated parietal endocarditis, such as those reported by Baümler[5] and by Loeffler.[30] Baümler described an extensive

whitening and thickening of the left ventricular endocardium especially near its apex, associated with mural thrombi and cardiac dilatation but without valvular lesions. The patients suffered from chronic congestive cardiac failure, especially from attacks of nocturnal dyspnea, and sometimes from an anginal syndrome. A review of the clinical histories and pathologic findings suggests that Baümler was dealing with healed myocardial infarction and fibrosis due to unrecognized, old, and possibly recanalized coronary artery occlusions. The resemblance to some of the cases of idiopathic hypertrophy and heart failure is also noted.

Loeffler[30] reported 2 cases of an afebrile parietal, fibroplastic endocarditis of both ventricles. There was an insignificant mitral valvulitis and insufficiency. The clinical picture, which resembled that of constrictive pericarditis, was characterized by persistent tachycardia, progressive evidences of visceral congestion, including enlargement of liver and spleen, serous effusions in the pleural cavity, subcutaneous edema of the lower extremities and finally ascites and edema of the upper extremities. The clinical manifestations were attributed to interference of the thickened, retracted endocardium with the inflow of blood into the right ventricle. A remarkable feature was the presence of an eosinophilia which in one case reached 70 per cent with a leukocytosis of 18,000.

OTHER ENDOCARDIAL LESIONS

A number of noninflammatory and degenerative endocardial lesions, especially of the valves, must not be confused with endocarditis. Certain hair-like *endocardial tags* such as the Lamblian excrescences from the nodulus aurantii may occasionally simulate endocardial vegetations.[17] They are composed of myxomatous or hyaline connective tissue without thrombus or associated valvular inflammation.

Yellow flecks or plaques of *atheromatous degeneration* are common on the ventricular surface of the anterior (aortic) cusp of the mitral valve. They are most frequent and prominent in the hearts of elderly and anemic subjects. They consist of collections of lipoid material, sometimes with calcium.

Valvular sclerosis is common. There may be only whitish plaques of valvular thickening occupying the distal portion of the leaflets, especially of the mitral valve. They consist of fibrous tissue. The atheromatous areas in the anterior mitral cusp may undergo fibrous replacement or occasionally calcification. These changes do not interfere with valvular function, for they are not extensive. Occasionally the ring of the mitral or aortic valve or both is infiltrated by a rigid incomplete collar of calcium (sclerosis annularis fibrosi—Dewitzky[9]). Ossification may occur. Calcification of the mitral or aortic ring may be denoted clinically by the presence of a loud, very harsh or musical systolic murmur. Histologically there is evidence that extensive fibrosis, hyalinization and occasionally elastification precede the deposition of calcium.

Calcification of valve cusps occurs usually when there is longstanding chronic rheumatic endocarditis. But occasionally calcification and consequent stenosis of the aortic valve may occur as a primary degenerative process[34, 15] (p. 604). In these cases, fibrosis and calcification begin in the arterial portion of the aortic valve near its base and extend from there to the sinuses of Valsalva (Mönckeberg's ascending sclerosis) or up the aortic leaflets until the whole valve is a hard, rigid mass with irregular calcific nodules and spicules which penetrate the ventricular surface (p. 605). In the fully developed stage it is

indistinguishable from the much more common calcific aortic stenosis of rheumatic origin. The roentgenologic diagnosis of calcification of the annulus fibrous, mitral ring and aortic cusps is discussed elsewhere (p. 612).

Endocardial pockets, also known as accessory leaflets, regurgitant pockets or birds' nests, are sclerotic thickenings of the mural endocardium, seen most often on the left ventricular septum below an insufficient aortic valve. They are believed to be due to tension of the regurgitant stream. Their openings are directed toward the aortic valve. Similar pockets, directed toward the apex, are found in the left atrium just above the mitral valve.

Among other regressive lesions are occasional instances of *mucoid* or *amyloid degeneration.*

Not uncommonly in the hearts of newborn or young infants, occasionally in those of children and rarely in the hearts of adults, are found single or multiple *endocardial blood cysts* or *tumors.* These are pink or dark red circumscribed nodules, chiefly on the leaflets of the mitral or tricuspid valves and composed of endothelial-lined lacunae of blood. They have been interpreted as hemangiomata or as hematomata.

Mural Thrombosis. Mural endocardial thrombi involving chiefly the left ventricle occur in cases of myocardial infarction. With extensive septal infarction mural thrombi may also develop in the right ventricle. Right ventricular mural thrombi have been described in certain rare cases of right heart hypertrophy of obscure origin. In cases of advanced congestive heart failure, especially with auricular fibrillation, mural thrombi may occur in any chamber, but predominantly in the atria and the atrial appendages. An underlying rheumatic atrial endocardial lesion may favor the development of mural thrombi. The thrombi may be of clinical importance because they are sometimes the source of systemic or pulmonary emboli.

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26

MITRAL VALVULAR DISEASE

Valvular heart disease is a major cardiac ailment which corresponds in incidence with its chief cause, rheumatic fever. Mitral valvular disease is most common, aortic stenosis or insufficiency next, while tricuspid disease occurs occasionally and pulmonic valvular disease rarely. Combined mitral and aortic disease is common in the rheumatic cases; in about 10 per cent, the tricuspid valve is also affected. The frequency of aortic insufficiency is increased in regions where syphilis is common.

Valvular heart disease is presented as a separate subject because it is often encountered when there are neither symptoms nor a history of the causative disease. Certain clinical features of valvular disease are identical and may be described in common, whatever the cause. Finally the disturbances in circulatory dynamics, the symptomatology and the type of heart failure are determined more often by the valvular lesion than by the disease which produced it. This is not to obscure the fact, however, that the presence of active rheumatic inflammation, the severity and extent of myocardial damage, the association of hypertension and the interference with coronary blood flow by arteriosclerosis or syphilitic ostial stenosis are vital factors which reduce the ability of the heart to tolerate the strain of valvular disease, and which may lead to heart failure.

ETIOLOGY OF MITRAL VALVULAR DISEASE

Rheumatic endocarditis is responsible for the great majority of cases of mitral valvular disease. In the early stages there is only insufficiency due to imperfect closure of the mitral orifice. Later a mitral stenosis develops, usually combined with some degree of insufficiency or regurgitation.[86] But often the physical signs and the cardiac disturbances are determined by the predominant mitral insufficiency or by predominant mitral stenosis.

Other rare causes of organic mitral insufficiency are bacterial endocarditis, traumatic rupture of a cusp or of the chordae tendineae, spontaneous rupture of the chordae, and rupture of a papillary muscle secondary to bacterial endocarditis or coronary occlusion.

Relative or functional mitral insufficiency occurs commonly as a result of pronounced dilatation of the left ventricle, usually in association with left ventricular failure. Imperfect valvular closure under such circumstances is due to dilatation of the mitral ring and to retraction of the cusps by the chordae and papillary muscles as the ventricular chamber elongates.

Mitral stenosis is almost always due to rheumatic endocarditis. Occasionally it is a congenital lesion[32, 44] due either to anomalous development or to fetal endocarditis, e.g., in the cases of Lutembacher's syndrome (p. 644). Functional mitral stenosis may result from obstruction of the valvular orifice by bacterial vegetations, atrial thrombi or tumors. Congenital mitral atresia has been described (p. 678).

Rheumatic mitral valvular disease occurs two or three times as frequently among females as among males.[109, 102]

PATHOLOGY OF MITRAL INSUFFICIENCY AND STENOSIS

Rheumatic Mitral Disease. The rheumatic valvulitis and verrucae lead to scarring, thickening, shortening and deformity of the cusps and retraction of their free margins.[27, 53] At the same time similar inflammatory changes and fibrosis cause thickening, fusion and shortening of the chordae tendineae. Incomplete closure of the mitral orifice with consequent mitral regurgitation results from the following:

1. Imperfect coaptation of the valve cusps because of their rigidity, deformity and retraction.
2. Fusion and shortening of the chordae which fix the cusps and restrain their apposition to each other, thus preventing closure of the valvular orifice in systole.
3. Inflammation and scarring of the mitral ring which dilate the orifice, and interfere with the muscular systolic reduction in its circumference, an important factor in its normal closure.

Mitral stenosis results from repeated rheumatic inflammation and healing. It is probable that at least two years are required for the development of mitral stenosis after the initial attack of rheumatic valvulitis. Mitral stenosis results from the following valvular abnormalities:

1. Fusion of adjacent leaflets to form a single circular curtain. The mitral opening may be further narrowed by continued contraction of the scar tissue and by subsequent calcification of the mitral ring and cusps.
2. Rigidity of the valve cusps, due to fibrosis. This keeps them fixed in a position which narrows the mitral orifice.
3. Fusion and shortening of the chordae tendineae and their absorption into the mitral cusps resulting in a funnel-shaped structure which accentuates the narrowing of the orifice. In other instances adhesion and shortening of the cusps produces a diaphragmatic slit described as the "button-hole" or "fish-mouth" type of mitral stenosis. Occasionally the term "tight" mitral stenosis is applied to those cases in which the mitral orifice only admits a probe.

Atherosclerotic (Calcific) Mitral Disease. Isolated white collagenous plaques of thickening and yellow atheromatous patches are almost always found in normal valves, even in those of children. More extensive degenerative changes occur with increasing age, especially on the ventricular surface of the anterior (aortic) mitral cusp.[58, 5] These lesions are of no clinical significance.

Calcification of the annulus fibrosus or ring of the mitral valve has been found in 10 per cent of hearts at necropsy, with greatest frequency among the aged and among women.[41] This lesion is clinically unimportant but may cause a loud, rough or musical apical systolic murmur and may be discovered by careful fluoroscopic examination.[45, 105] Usually calcification of the mitral ring

is of degenerative (arteriosclerotic) origin,[49, 82] and is not accompanied by calcification of the cusps. On the other hand, calcification of the valve cusps is almost always secondary to rheumatic inflammation.[93] Calcification of inflammatory origin may also involve the mitral ring. Calcification of the mitral ring or cusps may be associated with calcific aortic stenosis and occasionally with calcific deposits in the fibrous septum. The latter may damage the bundle of His and produce complete heart block or other disturbances in conduction.[119, 95, 115] The frequency of congestive heart failure, angina pectoris or conduction disturbances in cases of calcification of the mitral ring or cusps is due to associated rheumatic cardiovalvular disease or to coronary sclerosis and not to the direct effects of the calcium deposits.

Rarer Forms of Mitral Disease. *Bacterial endocarditis* (Chapter 34) may produce mitral insufficiency by perforation of a cusp, by formation of a valvular aneurysm, or by rupture of chordae tendineae or a papillary muscle. Functional mitral stenosis rarely results from obstruction of the orifice by cauliflower-like vegetations. I have seen an infected ball thrombus in the left atrium cause intermittent complete obstruction with shock and peripheral gangrene.[98] Syphilis (Chapter 35) rarely involves the mitral valve either as a gumma or by contiguous extension from a luetic aortitis.[104] The syphilitic myocarditis may simultaneously involve the bundle of His and produce heart block. Mitral stenosis due to tumors is discussed in Chapter 45.

Rupture of the mitral valve[10, 69] may cause mitral insufficiency by perforation or tear of a cusp or by rupture of chordae or a papillary muscle. Spontaneous rupture of chordae tendineae, usually of previously diseased valves, has also been noted.[7]

The Heart in Mitral Valvular Disease. The *left atrium* is considerably dilated and hypertrophied in both mitral insufficiency and stenosis. Sometimes it enlarges to giant proportions (aneurysmal dilatation of the left atrium), rarely attaining a volume of 2 or 3 liters.[12, 81] Rarely a giant left atrium erodes the spine at the level between D5 and D9.[6] In occasional cases of advanced mitral stenosis, no definite left atrial enlargement was found at necropsy but the heart in general, especially the right ventricle, was considerably enlarged.[50]

The *left ventricle* is dilated and hypertrophied in cases of predominant mitral insufficiency, or when prolonged mitral insufficiency precedes stenosis. As a rule, left ventricular hypertrophy is absent or slight because of the frequency with which stenosis develops in the rheumatic cases of mitral insufficiency. Left ventricular dilatation and hypertrophy may be very pronounced in cases of pure mitral insufficiency due to ruptured chordae.

In hearts with predominant mitral stenosis the left ventricle may be of normal size. But with pronounced and longstanding mitral stenosis, the left ventricle may become smaller than normal and even atrophic. The decreased size of the chamber is particularly confined to the posterior half or the so-called inflow tract.[68] An associated aortic valvular disease may produce enlargement of the left ventricle.

The *right ventricle* usually enlarges and becomes hypertrophied, especially after the development of pulmonary hypertension due to left atrial failure. The *right atrium* also becomes dilated with progressive right heart failure.

The Lungs in Mitral Valvular Disease. As a result of prolonged congestion and fibrosis the lungs become reddish-brown, firm, dense and dry ("brown

induration" of Virchow).[114] Infarcts due to pulmonary embolism, hemorrhagic areas due to rupture of small vessels and arteriosclerosis of the pulmonary arteries are also observed on gross examination.

The microscopic changes have been described by zu Jeddeloh[64] and by Parker and Weiss.[85] The alveolar walls are markedly thickened by interstitial edema, increased collagen and widening of the capillary basement membrane. The width of the alveolar wall may increase from a normal of 1 to 3 micra to 30 to 50 micra. "Heart failure cells," which arise from alveolar epithelium or reticuloendothelial cells and which contain brownish iron pigment derived from hemorrhage, are observed in the alveolar lumens. These cells are often extruded into the sputum. The capillaries become congested, wider than normal, elongated and beaded, and project into the alveolar lumens. These various changes interfere with pulmonary ventilation, by making the lung rigid and inelastic, and with diffusion and oxygenation of the blood, by widening the alveolar-capillary wall.

MITRAL INSUFFICIENCY

Pathologic Physiology

Compensation of the Left Atrium. Experimental studies[110, 78, 101] indicate that the normal ventricular output can be restored despite regurgitation into the left atrium of 50 per cent of the total stroke volume. The volume of blood in the left atrium during its diastole is greater than normal because of the regurgitant stream it receives from the left ventricle in addition to the usual inflow from the pulmonary veins. This results in increased left atrial pressure and increased stretch of the atrial musculature. The increased atrial pressure promotes the left atrial output during atrial diastasis. The increased stretch results in a stronger atrial contraction according to Starling's law of the heart. Thus the left atrium compensates for the mitral insufficiency by a greater output. But the greater diastolic volume and pressure in the left atrium lead to dilatation and hypertrophy of that chamber.

Compensation of the Left Ventricle. The enlarged output of the left atrium increases the diastolic volume and pressure of the left ventricle. This leads to a more forceful contraction and an augmented ventricular discharge of blood. In this manner the normal effective output into the aorta is restored, but the actual output is equal to the output into the aorta plus the regurgitant outflow into the left atrium.[116] An essential feature in left ventricular compensation is the speedy elevation of pressure during its isometric contraction, before there is any ejection or regurgitation of blood.[116] The increased diastolic volume and pressure in the left ventricle lead to dilatation and hypertrophy of this chamber. Thus compensation of mitral insufficiency is effected by dilatation and hypertrophy of both the left atrium and ventricle, but only at the expense of increased work for these chambers.

The Lungs and Right Heart. In pure rheumatic mitral insufficiency, compensation may be quite effective if the left atrial and ventricular musculature is not seriously damaged. Often, mitral stenosis eventually develops and some degree of pulmonary congestion occurs. When mitral insufficiency appears suddenly as a result of trauma or spontaneous rupture of the chordae tendineae, there is a rapid development of pulmonary congestion, hypertension of the

pulmonary circulation and right ventricular enlargement associated with heart failure.

Clinical Features

Mitral insufficiency includes three types of cases determined by the severity of the lesion and the state of compensation:

1. Mild Asymptomatic Cases. Many patients with mitral insufficiency are completely asymptomatic. In such cases the mitral valve may be moderately deformed without permitting any large reflux of blood. These patients may perform rigorous physical work without discomfort and often without awareness of any cardiac abnormality. Generally they do not develop cardiac failure but die of some intercurrent disease.

On *physical examination*, there may be only a loud, harsh or blowing systolic murmur near the apex, with varying extent of radiation toward the axilla. The left atrium and ventricle may be so little dilated and hypertrophied that the enlargement of these chambers cannot be demonstrated by percussion or roentgenologic examination. If the murmur first develops after an attack of rheumatic fever and persists, its organic nature may be presumed. If encountered accidentally, it may be indistinguishable from insignificant functional murmurs. If there is no history of rheumatic fever and no chamber enlargement occurs after a few years of observation, a definite clinical diagnosis is usually difficult. The importance of these asymptomatic cases lies in the occasional ones in which typical signs of mitral stenosis develop in the course of years.

2. Compensated Cases. In this group, the degree of regurgitation and the consequent compensatory enlargement of the left atrium and ventricle are sufficiently pronounced to permit definite diagnosis. Some degree of mitral stenosis may be associated, but mitral insufficiency is the dominant lesion. As in the first group of cases, compensation may be perfect and remain so for long periods during which there are no symptoms whatever, even with considerable physical effort. Often, however, there is some dyspnea on exertion, slight cyanosis, or evidence of engorgement of the pulmonary circulation, at least in its venous and capillary bed.

The *physical signs* include the systolic murmur due to the regurgitant stream of blood, and evidences of left atrial and ventricular enlargement. The apex beat is displaced outward and downward, and may be felt in the sixth interspace lateral to the left midclavicular line. Occasionally in cases of mitral insufficiency and stenosis associated with a huge left atrium which extends into the right chest, there may be a systolic propulsion of the right chest.[33] The maximal site of this pulsation is usually found in the right midclavicular line between the fourth and sixth rib. Occasionally extreme atrial dilatation causes a marked increase in the anteroposterior diameter of the thorax. *Percussion* may reveal enlargement of the left ventricle, but roentgenologic examination is required to demonstrate enlargement of the left atrium (p. 28). On *auscultation,* there is a loud, harsh or blowing murmur which may replace or follow the first heart sound, and which often extends throughout most of systole. The murmur is loudest at or near the apex and radiates into the axilla or less often toward the base of the heart or toward the back. The second pulmonic sound may be accentuated, but in children this may occur independently of the mitral disease.

In cases of ruptured mitral chordae tendineae, the systolic murmur is usually

loud, maximal at the apex and left sternal border, and associated with a thrill. There may also be an associated apical diastolic murmur.

3. Decompensated or Imperfectly Compensated Cases. Heart failure resulting from pure mitral insufficiency is uncommon, except in the cases due to spontaneous or traumatic rupture of chordae or cusps. In rheumatic cases failure may result from active rheumatic myocarditis, which severely damages the left ventricle upon which much of the compensation depends. This is most often seen in children. Occasionally failure is the result of an unusual strain, such as pregnancy and childbirth. In longstanding cases, a progressive mitral stenosis supervenes, with additional strain on the left side of the heart. The clinical picture is similar to that described under the decompensated stage of mitral stenosis.

Roentgenologic Examination of the Heart in Mitral Insufficiency. In the anteroposterior view, the lower left cardiac border, representing the left ventricle, extends abnormally outward and downward and may be unusually rounded. There may be a slight bump, due to a large left atrium, where the left ventricle approaches the junction to the pulmonary artery. The barium-containing esophagus is displaced to the right in anteroposterior views, and posteriorly in the right oblique view, by the curve of the enlarged left atrium. When failure supervenes, the pulmonary markings are increased because of vascular congestion, and the right cardiac contour is greatly widened because of right atrial and ventricular dilatation.

If the left atrium is of unusual proportions, as occasionally occurs in combined mitral stenosis and insufficiency, its shadow may appear along the right border. Then the right lower arch is due to the right atrium, and the right middle arch to the overlapping left atrium. These two arches may show pulsations in opposite directions, giving a see-saw effect. The upper pulsation (left atrium) expands laterally in systole due to the regurgitation of blood from the left ventricle; the lower (right atrium) moves medially in systole due to the transmitted pulsation of the right ventricle. The pulsation of the left atrium may be more readily seen by roentgenkymography or fluorocardiography.[74]

Electrocardiogram in Mitral Insufficiency. In contrast with the electrocardiogram of mitral stenosis, that of insufficiency shows a tendency to left axis deviation. The P waves may be tall and notched.

Diagnosis

The diagnosis of mitral insufficiency is based on the presence of a distinct apical systolic murmur and enlargement of the left atrium and ventricle. A history of rheumatic fever is supporting evidence. Demonstration of systolic expansion of the left atrium is also diagnostically important.

Not infrequently organic mitral insufficiency may be denoted by a systolic murmur without demonstrable cardiac enlargement. Thus Boone and Levine[20] observed 225 individuals with a history of rheumatic fever, with faint or distinct systolic murmurs but without cardiac enlargement. During an average observation period of 9.6 years, 42 per cent of those with a distinct systolic murmur developed mitral stenosis, aortic insufficiency or both, in contrast with 4.8 per cent of those with soft poorly transmitted murmurs. Similarly Kuttner and Markowitz,[70] after an eight year follow-up period, observed the development of definite organic heart disease in 48 per cent of 144 rheumatic children with a loud blowing apical systolic murmur but without cardiac enlargement, and in

13 per cent of 171 cases of potential or possible heart disease in which the murmur was soft and poorly transmitted. These observations suggest that in rheumatic patients a persistent distinct systolic murmur may be sufficient for the diagnosis of mitral insufficiency even when there is no cardiac enlargement.

The *diagnosis of mitral insufficiency due to nonrheumatic causes* is based on the sudden development of a loud apical systolic murmur in the course of bacterial endocarditis or myocardial infarction, after penetrating or nonpenetrating

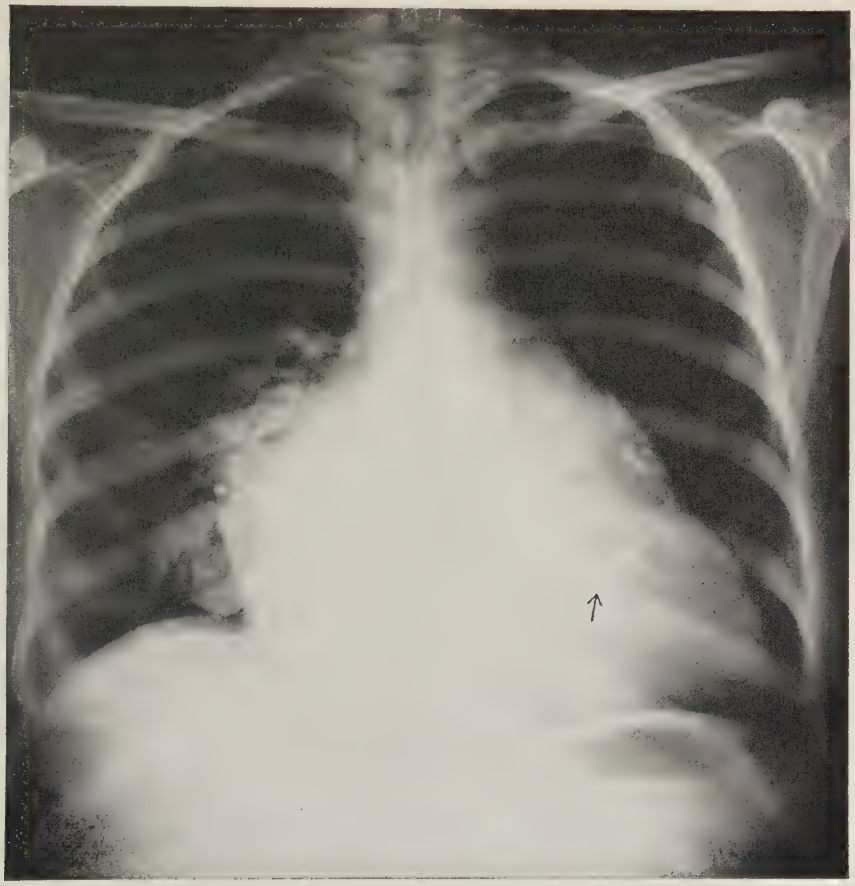


Fig. 58. Calcification of mitral ring. J-shaped density (arrow). Fluoroscopy and kymography revealed wide pulsations toward apex. Also calcification of pericardium.

chest injury, or after an unusual severe exertion. Spontaneous rupture of mitral chordae is suggested by the development in a middle-aged or elderly person, without striking cause, of a loud apical or left sternal murmur and thrill, followed in weeks or months by enlargement of the left atrium and ventricle and by congestive heart failure. Rupture of a papillary muscle is more likely to be followed by rapid heart failure, shock, acute pulmonary edema and death. Rupture of a congenital aneurysm of the sinus of Valsalva must also be differentiated (p. 664).

Relative or functional mitral insufficiency is suggested by the presence of an apical systolic murmur in a patient with hypertension or coronary artery

disease and heart failure. If the mitral murmur disappears with improvement of the circulatory status, the functional nature of the disturbance is confirmed.

Calcification of the mitral ring may be disclosed by a harsh or musical apical systolic murmur and by fluoroscopic visualization of a *U*- or *J*-shaped calcification in the region of the annulus fibrosus (Fig. 58).

Calcification of the mitral leaflets can be differentiated from calcification of the ring and almost always denotes organic rheumatic mitral insufficiency or stenosis.[35, 105, 18, 93] Calcification in the cusps appears fluoroscopically as groups of irregular nodular masses in the posterior third of the heart, moving downward toward the apex with ventricular systole.[61]

The Functional Systolic Murmur. The greatest problem in the differential diagnosis of mitral insufficiency is to distinguish an organic mitral murmur from a so-called functional one. A nonsignificant, physiologic or functional systolic murmur has been described in 30 to 90 per cent of children or adolescents;[111, 100, 80] often the murmur may be heard after exercise when it is absent during rest.[103] The incidence of functional systolic murmurs diminishes rapidly in adult life. That systolic murmurs often appear with anemia, fever and hyperthyroidism suggests that they result in these conditions from the increased velocity of blood flow. Many functional murmurs are of cardiorespiratory origin, arising as a result of compression of the overlying lobule of lung when the heart contracts. Chisholm[26] suggested that functional pulmonic systolic murmurs may occasionally be due to unequal stretching of the pulmonary artery with change of position, forced inspiration or as a result of pleural adhesions. Under these circumstances the valve cusps are apposed in such a way ("trigonoidation of the semilunar cusps") as to act as an obstruction to the outflow of blood.

Although there is no certain method of differentiating organic from functional murmurs, the following points are helpful: Functional murmurs are often loudest in the pulmonic area, radiate little and are faint in intensity. A close relation between the intensity of a systolic murmur and the presence of organic heart disease has been indicated by the studies of Freeman and Levine[46] and Baker et al.,[9] and by the above-mentioned observations of Boone and Levine[20] and of Kuttner and Markowitz[70] (p. 568). Cardiorespiratory murmurs disappear when the breath is held. Organic murmurs usually disclose both high and low frequency vibrations in the phonocardiogram, while functional murmurs are of uniform pitch.[11] These differences permit a statistical differentiation of organic from functional murmurs when dealing with large numbers of persons but are not decisive in the individual case.

For practical purposes it is important to view all systolic murmurs with suspicion and to attempt to determine their cause. This viewpoint often leads to the discovery of rheumatic mitral valvular disease or calcific aortic stenosis, sickle-cell or other anemia, hyperthyroidism or hypertension. Not infrequently, especially in older individuals, the finding of an apparently insignificant systolic murmur suggests the possibility of subacute bacterial endocarditis when the diagnosis otherwise appears obscure. In young persons without a history of rheumatic fever and without cardiac enlargement or other evidences of cardiovascular disease, care must be taken not to make a diagnosis of organic heart disease lest cardiac invalidism or cardiac neurosis be initiated, even though a certain percentage of such individuals will eventually disclose unmistakable valvular heart disease. Under the circumstances mentioned,

restriction of activity is rarely indicated. On the other hand, the realization that many individuals with apparently nonsignificant systolic murmurs have organic valvular disease poses a different problem when deciding whether to accept such applicants for life insurance or military service.

MITRAL STENOSIS

Pathologic Physiology

Compensation by the Left Atrium. In animal experiments[59, 2, 101] significant circulatory disturbances occur only when the mitral orifice is narrowed to less than one quarter of its normal size. The inflow into the left ventricle and the left ventricular stroke output are temporarily diminished but are soon restored in the following manner:

1. The residual blood in the left atrium plus the normal inflow from the pulmonary veins increases the diastolic volume and diastolic pressure in that chamber.
2. The elevated pressure head in the distended left atrium increases the ventricular inflow during early diastole.
3. In late ventricular diastole the heightened diastolic tension in the left atrium leads to a more forceful atrial contraction and a greater discharge into the left ventricle (Starling's Law of the Heart).

The effectiveness of left atrial compensation is limited because of its relatively weak musculature, by the frequent active or inactive lesions of rheumatic fever in this chamber, and often by the development of atrial fibrillation. Consequently, compensation in mitral stenosis is less effective than in mitral insufficiency in which the powerful left ventricle as well as the left atrium plays a significant role.

The Pulmonary Circulation and Right Heart. The above-mentioned limitations in left atrial compensation as well as the absence of valves between the left atrium and pulmonary veins account for the early occurrence of pulmonary congestion in cases of mitral stenosis. Eventually there is an elevation in pressure in the pulmonary artery as can be determined clinically by intracardiac catheterization. The increased pressure in the pulmonary circuit produces slight or moderate dilatation and hypertrophy of the right ventricle in the same manner that essential (systemic) hypertension causes hypertrophy of the left ventricle. A pronounced rise in pulmonary arterial and right ventricular pressure occurs only with advanced left atrial failure. This is followed eventually by increasing pressure, dilatation and hypertrophy of the right cardiac chambers.

Clinical Features of Mitral Stenosis

1. Stage of Complete Compensation. Cardiac symptoms may be completely absent in patients with physical signs of mitral stenosis, although this occurs less frequently than in mitral insufficiency. In these patients, the mitral obstruction is of slight or moderate degree and compensation is perfect.

The perfectly compensated, asymptomatic patient with mitral stenosis may live a normal life span and engage in normal physical activities. But he is subject to the same complications as patients with severer mitral lesions. Repeated rheumatic infections, progressive contraction and adhesion of a scarred valve, or secondary calcification may intensify the obstruction and produce

circulatory disturbances in a patient hitherto asymptomatic. A patient with mitral stenosis may suddenly develop symptoms of pulmonary congestion or right heart failure after a prolonged period of perfect compensation. Bacterial endocarditis, auricular fibrillation, embolization, pulmonary infections and acute pulmonary edema may suddenly abbreviate a previously uneventful course.

2. Stage of Left Atrial Failure. The majority of clinically significant cases of mitral stenosis are those in which compensation is imperfect and there are evidences of pulmonary congestion. In these cases we may speak of failure of the left atrium, for this chamber, although dilated and hypertrophied, is no longer able to eject or accommodate the excess of blood dammed up behind the mitral obstruction. The lungs undergo alterations which interfere with gaseous exchange and diminish the vital capacity. When this occurs, the disease is no longer asymptomatic. Some degree of decompensation is a common and early development in patients with mitral stenosis, because the weak left atrium can rarely prevent pulmonary congestion for long. When this congestion is slight or moderate, the patient may suffer hardly any discomfort unless he attempts some unusual physical task. Thus the degree of left atrial failure and consequent pulmonary congestion is very variable and the distinction between compensation and decompensation in mitral stenosis may not be a sharp one.

The following are the chief manifestations of mitral stenosis in the stage of left atrial failure, but some of them may occur when the lesion is seemingly well compensated or at any stage of the disease.

Dyspnea and *cyanosis* are the major symptoms of mitral stenosis. They result from pulmonary congestion due to failure of the left atrium. A mild degree of cyanosis produces early the so-called mitral facies. This is characterized by a cyanotic flush over the cheekbones and a dusky cyanosis of the lips, which may be more striking following exertion. Severe degrees of cyanosis are seen in longstanding cases of mitral stenosis and pulmonary congestion with marked alterations in pulmonary structure.

Shortness of breath is the commonest complaint in mitral stenosis and the one most disturbing to the patient. Almost invariably the dyspnea is induced by exertion. Rarely is it of the paroxysmal nocturnal variety encountered in the left ventricular failure of aortic, hypertensive or coronary artery heart disease. Many patients with mitral stenosis become so accustomed to a mild degree of chronic exertion dyspnea that they are hardly aware of its existence. Occasionally, shortness of breath is precipitated acutely, perhaps by arduous exertion, an infection, pregnancy or the onset of auricular fibrillation. Eventually dyspnea may be present even at rest. At this stage, *orthopnea* is generally associated.

Palpitation and precordial distress are early symptoms, which occur almost as frequently as dyspnea. They are not directly due to the pulmonary engorgement. Palpitation is especially disturbing at night when the patient may be unable to fall asleep, or may be awakened suddenly to become aware of forceful or rapid heart beats which occasionally skip. Palpitation may be due to extracardiac factors such as indigestion, excessive coffee, alcohol or tobacco, exertion or excitement, but it appears to be induced by these causes much more readily in the heart with mitral disease than in the normal one. The onset of auricular fibrillation may be heralded subjectively by palpitation and

precordial distress, but when the fibrillation is established and associated with a slow ventricular rate, many patients are either unaware of or undisturbed by its presence.

Hemoptysis has been encountered in 10 per cent of cases of mitral stenosis.[118] It may occur late in the disease or it may be the initial and only subjective complaint. Usually it denotes advanced mitral stenosis. It may occur suddenly and be of considerable severity. In 3 cases reported by Oppenheimer and Schwartz[83] and in 6 by Guizetti and Dinkler,[54] the volume of a given hemorrhage amounted to between 200 and 300 cc. I have seen repeated brisk hemoptysis produce a marked secondary anemia in a woman with mitral stenosis who was otherwise asymptomatic. Other possible causes of hemoptysis and of secondary anemia had been thoroughly excluded. Recently I saw a man with mitral stenosis in whom a bronchial carcinoma had been diagnosed and another who was suspected of having pulmonary tuberculosis because of cough and hemoptysis. In both, increased pulmonary markings due to vascular congestion had been misinterpreted as parenchymal lesions. The typical mitral stenotic murmur had apparently been overlooked because it was clearly audible only when the patients lay on their left side.

Hemoptysis may occur repeatedly with moderate pulmonary engorgement and be absent when pulmonary stasis is severe. Usually, however, it is more apt to occur with increasing pulmonary congestion. In the cases reported by Oppenheimer and Schwartz,[83] the attacks of hemoptysis were preceded by aura with psychogenic manifestations and pain between the shoulder blades. The hemoptyses are not in themselves fatal and subside within a few days, but the ultimate prognosis in these cases is usually poor. Hemoptysis has been attributed to the rupture of small congested capillaries or small vessels in the lung (pulmonary "apoplexy"). But according to Ferguson et al.[40] the bleeding arises from the rupture of varices of the bronchial veins. These varices result from pulmonary congestion and consequent enlargement of the communications between the pulmonary and bronchial veins. Hemoptysis may also be due to pulmonary embolization and infarction. This usually occurs in patients with severe pulmonary stasis, right heart failure and auricular fibrillation.

Cough is a frequent symptom. It is usually worse at night and after physical exertion. As a rule it is due to pulmonary congestion and occasionally, in part, to pressure of a large left atrium on the bronchial tree. Occasionally cough is the most prominent symptom of the disease.[66] Most often the cough is nonproductive, but sometimes there is an associated mucoid or mucopurulent expectoration due to secondary bronchial and pulmonary infections, which are prone to complicate pulmonary congestion in mitral stenosis. The sputum frequently contains numerous "heart failure" cells.

Acute pulmonary congestion or edema occurs occasionally in mitral stenosis[47, 96, 43] but it is much less frequent than in aortic valvular lesions. It may occur in patients with auricular fibrillation or with sinus rhythm.[13] The occurrence of the attack is less sharply limited to the night and the horizontal position than in cardiac "asthma" due to left ventricular failure. As a rule it follows sudden or severe exertion, intercourse or bathing and may develop during operations, pregnancy,[22] childbirth or after rapid digitalization. It has also been precipitated by attacks of paroxysmal tachycardia[79] or by the intravenous administration of salt solution.[88]

The most plausible explanation for its occurrence is the sudden intensifica-

tion of pulmonary stasis in an already congested lung, due to an increase in venous return to and output from the right heart. A relatively competent right heart appears essential to its development, but occasionally there are mild evidences of right heart failure. That acute pulmonary edema occurs so much less frequently in the pulmonary congestion of mitral stenosis than in that of left ventricular failure may be due to the more gradual development of pulmonary congestion in the former and consequently to differences in pulmonary accommodation. Diminished permeability of thick capillaries may be a factor.

Angina Pectoris. Vague precordial sticking or aching sensations occur occasionally in mitral stenosis. Most often they are due to extracardiac causes or to a superimposed neurosis. Definite angina pectoris with typical precordial and arm radiations occurs occasionally[16, 25] and is probably due to associated aortic or coronary artery disease.[72] Explanations which attempt to relate angina pectoris to pressure of a large left atrium on a coronary artery[108] or to narrowing of the coronary ostia by traction of shortened chordae[60] appear untenable.

Hoarseness and paralysis of the left recurrent (laryngeal) nerve were first described by Ortner[84] in two cases of mitral stenosis. The hoarseness may be intermittent at first. Later it becomes constant and may progress to complete aphonia. The most plausible explanation of this symptom appears to be that of Fetterolf and Norris,[42] who concluded from detailed anatomic studies that the left recurrent nerve is compressed between the dilated left pulmonary artery and the aorta or aortic ligament.[3, 112] Paralysis of the laryngeal nerve and left vocal cord also occurs in other cardiac conditions associated with dilatation of the pulmonary artery.[31]

Dysphagia is an uncommon symptom resulting from pressure of a dilated left atrium on the esophagus.[113]

Weakness is a common complaint in mitral stenosis with failure, just as it is in other forms of valvular disease. *Menstrual disturbances*, especially irregularity, oligomenorrhea or amenorrhea, are frequently encountered in women with mitral disease.

Arrhythmias occur frequently both in this stage and when the right ventricle fails. *Auricular fibrillation* is the most important of these. De Graff and Lingg[30] encountered it in 43 per cent of 644 patients with mitral stenosis, who were followed to their termination. Its development is denoted symptomatically by palpitation, less often by precordial distress and dyspnea. It may be preceded by other irregularities, such as extrasystoles or auricular flutter. The fibrillation may be paroxysmal or persistent. Usually paroxysmal fibrillation is converted into the permanent form. It may herald the onset of right heart failure, or it may actually precipitate it. There is evidence that the cardiac output is diminished 20 to 25 per cent when auricular fibrillation occurs in patients with mitral stenosis.[67] On the other hand clinical experience indicates that usually cardiac efficiency is not appreciably better with normal rhythm than with auricular fibrillation, provided the ventricular rate can be kept slow. Auricular fibrillation, like right heart failure, is an end stage in mitral stenosis. Occasionally, auricular fibrillation with slow ventricular rate is compatible with five or more years of life.

Paroxysmal tachycardia and extrasystoles are seen frequently in patients with mitral stenosis, but they are not characteristic of this lesion, as is auricular fibrillation.

3. Stage of Right Heart Failure. Right heart failure is a common termination

of mitral stenosis. The longstanding increase of pressure in the pulmonary circulation, as indicated anatomically by severe sclerosis of the pulmonary vessels, leads to dilatation and hypertrophy of the right ventricle. Failure of this chamber results in part from the mechanical effect of the increased strain, and in part from the myocardial disease, which is generally of rheumatic origin. The precipitating causes have been discussed elsewhere (p. 54).

The symptoms of right heart failure may develop gradually or suddenly. Usually they follow a period dominated by symptoms of pulmonary engorgement. Exertional dyspnea becomes more severe and breathlessness is present even at rest. Orthopnea may be a prominent symptom. Not infrequently, when right-sided failure is well developed, the dyspnea and orthopnea are alleviated due to the diminished right ventricular output into the pulmonary circulation. But when severe changes in the lungs are fully established as a result of longstanding mitral stenosis, the dyspnea and orthopnea may remain unabated even when the right ventricle fails. Cyanosis similarly persists with the development of right heart failure.

Certain additional symptoms are intrinsic in right heart failure and result from engorgement of the systemic venous system (Chapter 5). These include engorgement of the cervical and other superficial veins, enlargement of the liver, peripheral subcutaneous edema and transudates in the serous cavities.

Auricular Thrombosis. Auricular thrombi may occur at any stage of mitral stenosis, but they are especially frequent after right heart failure and atrial fibrillation develop. These antemortem clots depend chiefly on the stagnation of blood in a very large atrium, but rheumatic endocardial lesions may predispose to their formation.[51] The thrombi are found in either atrium, and especially in the auricular appendages. In the absence of right heart failure and consequent dilatation of the right atrium, the thrombi are usually confined to the left atrium. They occur as small brownish-red ovoid masses of organized platelet thrombi attached to the pectinate muscles and endocardium. Occasionally they are large, spherical or polypoid purplish masses, with smooth surface and gelatinous structure, which partially or completely fill the atrial chamber.

Clinical symptoms are not an invariable consequence of the auricular thrombi, which may be accidentally discovered post mortem. Frequently, however, they produce serious clinical disturbances either by (1) embolic closure of distant vessels or (2) local obstruction of the stenotic mitral orifice.

1. Embolization. Fragmentation or erosion of auricular thrombi results in dissemination of small particles, which produce embolic closure of pulmonary, cerebral, visceral or peripheral arteries. Cookson[28] found that cerebral embolism with hemiplegia occurred with equal frequency in patients with auricular fibrillation and those with regular sinus rhythm. De Graff and Lingg[30] found that embolism and infarction were somewhat more frequent among patients with auricular fibrillation. Pulmonary emboli with infarction of the lung occurred in almost half of the patients I have seen with mitral stenosis and right heart failure. In these cases the source of the emboli may be thrombi either in the right auricle or in the peripheral deep veins of the lower extremity. Pulmonary infarction is one of the complications to be considered when cardiac failure does not yield to treatment.

Several times I have observed the sudden occurrence of cerebral emboli in well compensated patients with mitral stenosis. I have also seen cerebral em-

bolization as the first clue to the presence of mitral stenosis. Frequently the right middle cerebral artery is occluded, with resultant aphasia and crossed hemiplegia.[57] Sometimes these hemiplegias are relatively benign in that they clear up with only slight disability in the patient. But they are usually forerunners of further embolization. A small cerebral artery may be occluded, and only a focal paralysis or isolated aphasia is observed.

Visceral embolization is not infrequent, especially in the kidney and spleen. Infarcts in these organs are most often discovered accidentally post mortem, but clinical symptoms may occur. I have also seen embolization of the hepatic artery with infarction of a lobe of the liver. Of greater clinical importance is embolization of a mesenteric artery with infarction of the intestinal wall. I have twice seen patients with infarction of the ileum operated upon for suspected acute appendicitis.

Embolization of peripheral arteries is not rare. Usually it produces dramatic clinical symptoms because of the abruptness of the occlusion and the absence of adequate collateral circulation. Embolization of the aorta with formation of a pantaloon thrombus at its bifurcation may cause sudden sharp pain in the abdomen, lower back and extremities, loss of pulsation and warmth of the lower extremities and shock. More localized symptoms occur with embolization of the popliteal, femoral or brachial arteries. Gangrene may result and amputation may be necessary. Occasionally recovery follows such amputation, but usually the general condition of the patient or subsequent emboli in other parts of the body cause death. I have also seen spontaneous recovery from peripheral embolization without the development of gangrene.

2. Ball-Valve Thrombus. The large ball-shaped thrombi may completely occlude the mitral orifice[1, 38, 39] and produce sudden death.[65, 4, 48] I have also seen occlusion occur more gradually and lead to distinctive clinical features which make possible an antemortem (usually preterminal) diagnosis of this complication. The patient develops a cadaveric, mottled, cyanotic discoloration of the hands and feet. The ends of the extremities, the tip of the nose and the ear lobes become cold and streak with blue, and undergo local necrosis. The pulse may be weak or absent. Within a few days the patient goes into shock and dies. All of the patients studied by Schwartz and Biloon[99] had auricular fibrillation with rapid ventricular rate, and were refractory to digitalis.

Occasionally there is intermittent occlusion as the thrombosis is floated away from the orifice either by the blood stream or by change in the patient's position. With recurrent occlusion there is an exacerbation of symptoms, especially dyspnea and cyanosis, syncope and sometimes disorientation, convulsions or transient shock. Relief may occur spontaneously. Sometimes the patient learns to obtain relief by sitting up and leaning forward. Ernstene and Lawrence[37] reported a case in which there was a typical attack of cardiac asthma.

Physical Signs in the Heart. *Inspection.* In children the precordium may bulge. There may be a visible pulsation in the epigastrium and to the right of the sternum if right ventricular hypertrophy has occurred.

Palpation. A characteristic *presystolic thrill* may be felt as a purring sensation on the surface of the precordium in the region of the apex.

A palpable *shock* may accompany the first sound at the apex and the second sound in the pulmonic area. In addition, one can sometimes feel a *tap* in the apical region, immediately after the second sound. This is the palpable equiva-

lent of the sound produced by the opening snap of the rigid stenotic mitral valve (see below).

The apical impulse is usually felt at its normal site as a hurried slapping stroke. A tentative diagnosis of mitral stenosis can sometimes be made on palpation, which may reveal a rapid, slapping apical impulse, a presystolic thrill, a diffuse precordial impulse, and a palpable shock over the pulmonary region and apex.

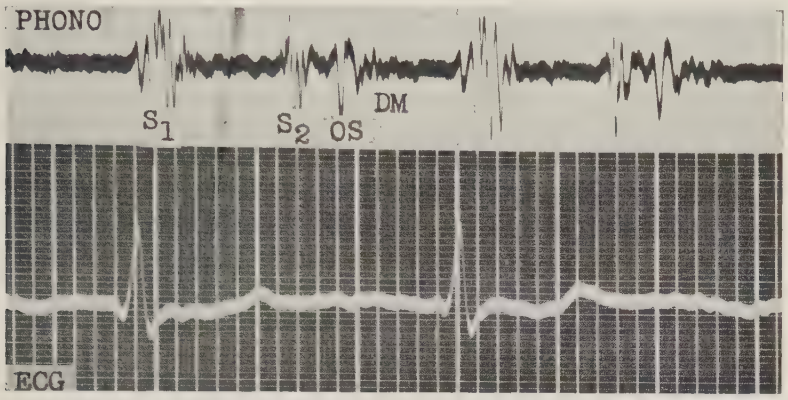


Fig. 59. Mitral stenosis. Opening snap (OS) with diastolic murmur (DM). Absence of presystolic murmur related to atrial fibrillation.

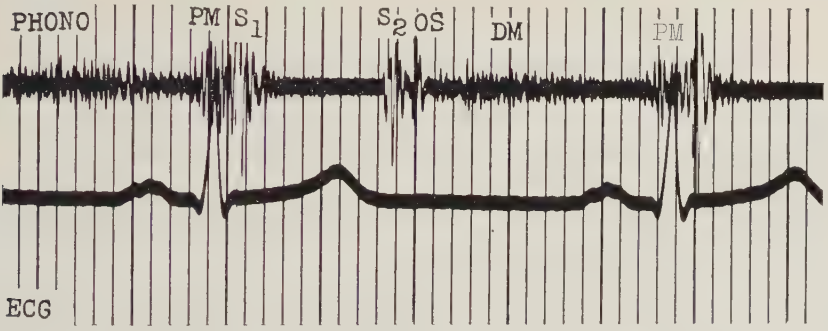


Fig. 60. Mitral stenosis. Opening snap (OS) and decrescendo diastolic murmur (DM) followed by crescendo presystolic murmur (PM).

Percussion. Prominence of the pulmonary artery may cause increased cardiac dullness along the left border, at the level of the third interspace and fourth rib.

Auscultation. The auscultatory signs of mitral stenosis are frequently confusing because they vary greatly with the severity of the lesion at different stages of the disease. Over long periods of time they may alter considerably even in the same patient, because the valve may be undergoing progressive change as a result of recurrent inflammation and healing.

The characteristic sign is a localized apical *diastolic murmur* (Fig. 60). This may be entirely presystolic in time, or it may fill most or all of diastole, with accentuation in presystole (Fig. 60), or it may occur in the early or middle period of diastole and completely lack a presystolic element. The presystolic

accentuation may disappear with auricular fibrillation or heart failure (Fig. 59). The diastolic murmur arises as a result of an extremely rapid blood flow past the mitral obstruction into the left ventricle. It occurs during those portions of diastole when the pressure difference between the left atrium and left ventricle becomes especially high. This pressure difference is accentuated by atrial contraction, especially when the left atrium undergoes compensatory dilatation and hypertrophy. The theory that the presystolic murmur is really a systolic regurgitant murmur of mitral insufficiency[23] appears untenable.

The *presystolic murmur,* which in itself suggests the diagnosis of mitral stenosis, is low pitched and rumbling or rolling in quality, with a characteristic crescendo accentuation which merges into a "snappy" or booming first sound. This murmur is sometimes described as a mid-diastolic roll with presystolic accentuation. Graphic registration of the heart sounds indicates that the crescendo effect is not part of the murmur itself but only an auditory illusion created by the proximity of the murmur to the subsequent sharp first sound.[73] The murmur is usually well localized just within the apex in an area which is not much larger than the bell of a Bowles stethoscope. Thus it can be easily overlooked unless the region of the apex is completely examined. Its small area of audibility corresponds to the small portion of left ventricle applied to the chest wall, while its radiation toward the left atrium is not heard, since that chamber is situated posteriorly, deep in the chest wall. Often the presystolic murmur is heard only if the patient is in the left lateral position. Sometimes it is demonstrable only if the cardiac rate is quickened by exercise, emotion or the administration of amyl nitrite.

The characteristic presystolic murmur is often absent in mitral stenosis. On the other hand its presence does not always signify that lesion:

1. It is absent in mild cases, or early in the disease, when the obstruction is relatively insignificant. It disappears in the late stages of mitral stenosis if auricular fibrillation sets in or when the left atrium becomes extremely dilated. The early diastolic murmur, however, remains and occupies a variable part of diastole. The diastolic murmur may be misinterpreted as presystolic, in cases with auricular fibrillation, if the ventricular rate is rapid and the murmur is close to the first heart sound.

2. A typical presystolic murmur may be encountered in aortic insufficiency with a normal mitral valve[89] (Austin Flint murmur, p. 594). Recently Bland, White and Jones[17] noted that a rumbling mid-diastolic or presystolic murmur occurred in children and young adults with recent, severe, active rheumatic carditis and ventricular dilatation, in whom postmortem examination revealed no mitral stenosis. A presystolic murmur has been described also in some cases of severe secondary anemia and cardiac dilatation due to ancylostoma (hookworm) infection,[55] and in cases of pernicious anemia and sickle-cell anemia (Chapter 43). A transient mid-diastolic apical murmur has been noted in some cases of acute nephritis with hypertension and left heart failure.[91]

The *first sound* at the apex is almost as characteristic as the presystolic murmur. It is short, snapping (or "snappy"), loud and booming, and accompanied by a palpable apical shock. It is usually an early sign and may be noted before there is any diastolic murmur. Its shortness and loudness have been explained as being due in part to the fibrotic changes in the valve cusps and chordae tendineae, but especially to the rapid contraction of the left ventricle (as

a result of the abbreviation of systole). A similar booming first sound may be heard in Graves' disease, where there is diminished ventricular filling due to tachycardia. When the mitral valve becomes completely rigid and immobile, the sharp first sound disappears.

The *second sound* heard over the pulmonic area is accentuated and like the first sound at the apex may be accompanied by a palpable shock. The accentuated pulmonic second sound is due partly to the rise of pressure in the pulmonary artery and partly to the rotation of the pulmonary artery and conus, which brings them closer to the chest wall. The pulmonic second sound may be *reduplicated* as well as accentuated. The pathogenesis of this reduplication is uncertain, but may be the change in the relative pressures in the pulmonary artery and aorta with resulting asynchronous closure of the semilunar valves.

The *second sound at the apex* may appear reduplicated, since it is often followed immediately by a click which is palpable as well as audible. This is caused by the sudden recoil of the resistant mitral cusps as they are opened by the strong atrial stream. It has been termed the "opening snap" or the "claquement d'ouverture" of the mitral valve (Figs. 59–60). While it has long been recognized by continental writers, its frequent occurrence has recently been emphasized in this country by Margolies and Wolferth,[77] who made detailed phonocardiographic studies. They demonstrated that this third apical sound occurred usually between 0.06 and 0.11 second after the second sound, which confirms the concept that it is connected with the opening of the mitral valve. This extra click may be quite loud and produce an echo effect which the French have termed "bruit de rappel." The opening snap may be misinterpreted as a normal third heart sound, as a gallop rhythm or as a split second sound. The occurrence of an extra sound at the apex in a young individual without failure and especially with a history of rheumatic fever should always suggest the possibility of mitral stenosis.

An apical systolic murmur is frequently present due to significant mitral regurgitation.

Functional Pulmonic Insufficiency. In addition to the apical diastolic murmur in mitral stenosis described above, occasionally a soft-blowing diastolic murmur is heard over the pulmonic area. This was described in 1889 by Graham Steell as "the murmur of high pressure in the pulmonic artery" and is known as the Graham Steell murmur.[107] It is probably the result of a functional insufficiency of the pulmonic valve due to pulmonary artery hypertension and consequent dilatation of that vessel and of the pulmonic orifice.[87, 97] Rheumatic inflammation of the base of the pulmonary artery and valve and atherosclerotic changes in the vessel may play an accessory role in its dilatation.[75] While relative pulmonic insufficiency and the Graham Steell murmur are encountered most often in mitral stenosis, they may also occur in various chronic pulmonary diseases associated with increased pressure in the pulmonary circuit. The Graham Steell murmur must be distinguished from the diastolic murmur of aortic insufficiency. The latter is characterized by differences in the roentgenologic appearance of the heart and by distinctive peripheral signs.

Pulse and Blood Pressure in Mitral Stenosis. In compensated mitral stenosis, the *pulse* is generally normal. In extreme stenosis, the pulse may become soft and small, corresponding to a diminished stroke output. Late in the disease,

especially during the stage of right heart failure, the pulse is often completely irregular due to auricular fibrillation. Extrasystoles and dropped beats are not infrequent at various stages of mitral stenosis.

The *blood pressure* in mitral stenosis is either normal or slightly diminished. The pulse pressure may also be somewhat less than normal. The occasional reduction in blood pressure and pulse pressure probably reflects a slightly di-



Fig. 61. Mitral stenosis. Prominent left pulmonary segment. Large hilar and pulmonary vessels. Chronic pulmonary congestion with finely mottled or nodular densities in both lung fields. Limited cardiac reserve but no overt physical or other signs of heart failure.

minished stroke output. Maintenance of blood pressure despite a diminished cardiac output has been ascribed to a compensatory vasoconstriction. In heart failure there may be an elevation of pressure ("Hochdruckstauung"), especially the diastolic pressure, which falls to its former level with improved circulatory function. More often there is a fall in systolic blood pressure and pulse pressure when failure occurs.

With advancing age, patients with mitral stenosis were said to develop *hypertension* more frequently than control groups.[19, 71] However, this alleged relationship has been doubted.[24, 62]

Roentgenologic Appearance of the Heart in Mitral Stenosis. The roentgeno-

logic appearance of the heart in mitral stenosis varies with the stage or severity of the lesion.

1. In cases of early or mild mitral stenosis, the cardiac size and outlines are often normal.[36] If some left atrial dilatation and hypertrophy are present, they are difficult to demonstrate.

2. More advanced cases reveal evidence of enlargement of the left atrium and occasionally of the right ventricle.

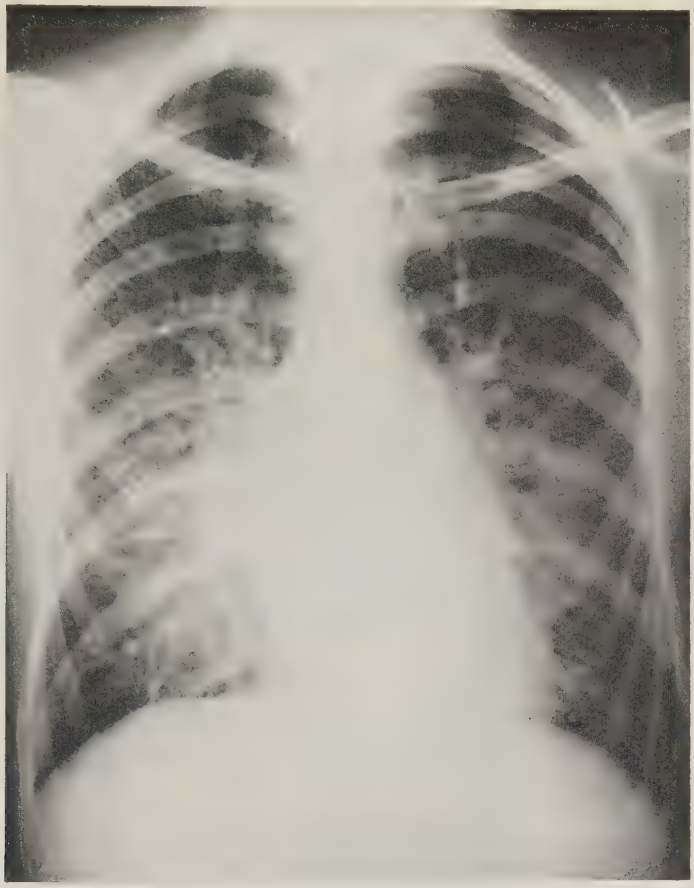


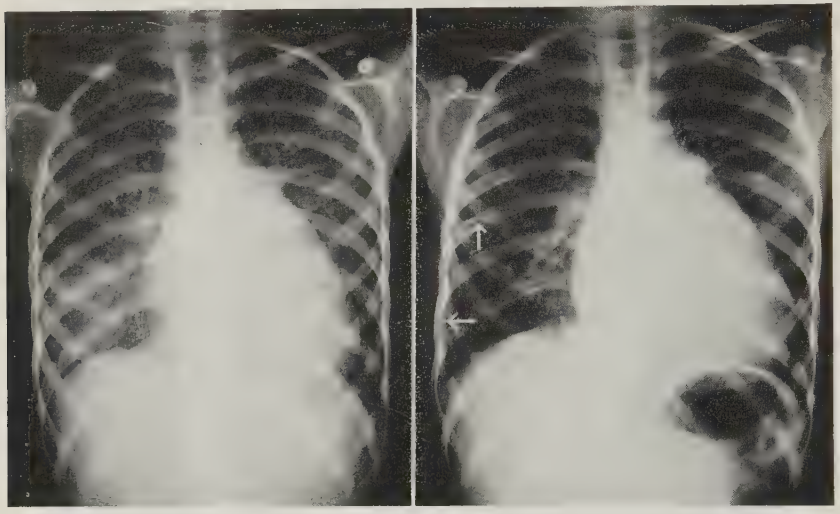
Fig. 62. Mitral stenosis with pulmonary edema. Diffuse haziness of lung fields with prominent pulmonary vessels and radiating streaks. Tendency to involve medial fields with clearing at periphery.

(a) Left atrial enlargement (p. 28) is characterized by encroachment on the retrocardiac space and posterior displacement of the barium-containing esophagus, as seen in the right anterior oblique view (Fig. 8*B*, p. 27).

(b) In the posteroanterior view the left-sided waist of the heart is filled out; there is a straightening or convexity of the left middle cardiac contour due to enlargement of the left atrium and increased prominence of the pulmonary artery and its left main branch (Figs. 8*A*, p. 27, and 61). The latter results chiefly from elevation and elongation of the pulmonary artery[52] by the left atrium and enlarged right ventricle, and slightly from dilatation of the artery.

This straightened or convex left border gives the cardiac silhouette its so-called "mitralized configuration." But a similar appearance may be encountered in other conditions associated with pulmonary hypertension. When the left atrium is extremely large it may form a second bulge on the right border just above the right atrial segment, or it may rarely form the entire right cardiac border (Fig. 10, p. 29). The enlarged hypertrophied left atrium may appear as an increased density within the shadow of the heart. In the posteroanterior view the barium-containing esophagus is seen to be displaced to the right (Fig. 9, p. 28). The left main bronchus is elevated toward the horizontal position (Figs. 9 and 10, pp. 28 and 29).

(c) In the left oblique view the enlargement of the left atrium may splay the main bronchus[106] and compress and elevate the left one. Displacement of



A B

Fig. 63. *A*, Mitral stenosis. Pulmonary infarction in right middle lobe, with small pleural effusion. Upper border of infarct delimited by transverse fissure.

B, Three months later. Infarct cleared. Residual thickening of right transverse fissure (upper arrow) and vertical band of pleural thickening along lower right chest wall (lower arrow).

the right chambers by the large left atrium may cause an enlargement of the cardiac shadow to the right and anteriorly, in this view.

Right ventricular enlargement is not prominent and may be revealed by anterior encroachment on the retrosternal space, in the right lateral view. The aortic knob is small in contrast with the prominent pulmonary artery.

3. With advanced mitral stenosis and heart failure the above alterations become accentuated. In addition the right cardiac border is displaced to the right by enlargement of the right atrium or by displacement of this chamber by the enlarged right ventricle and left atrium. The left cardiac border may also be displaced to the left by enlargement and rotation of the right ventricle, which may come to form the apex of the heart. The transverse diameter of the heart is enlarged.

The pulmonary vessels, especially at the hilum, become more prominent and the pulmonary fields congested (Fig. 61). Occasionally there is an acute

increase in the degree of pulmonary congestion with consequent pulmonary edema (Fig. 62). Pulmonary infarction occurs commonly (Fig. 63). In long-standing cases of mitral stenosis and pulmonary congestion, nodular densities or reticular areas may appear resembling miliary tuberculosis, sarcoidosis, pneumoconiosis[94] or carcinomatosis.[63] Sometimes these disseminated nodules are calcified or even ossified.[31] They may contain hemosiderin deposits.

The above configurations may be modified by associated lesions, notably by left ventricular enlargement in aortic insufficiency or to a lesser extent in mitral insufficiency.

The Electrocardiogram in Mitral Stenosis. The P waves in leads I and II are often widened, notched and may be of increased voltage, presumably due to enlargement and hypertrophy of the left atrium[14, 117] (Fig. 18*A*, p. 42). There is usually right axis deviation with evidence of right ventricular strain (p. 41) (Fig. 17, p. 39). Occasionally there is evidence of right bundle branch block.[90] Auricular fibrillation is frequent in advanced cases. If aortic valvular disease is associated there may be no axis deviation or deviation to the left.

Complications of Mitral Stenosis. These occur so frequently that they have been described as features of the disease. For convenience they are recapitulated here:

(1) Cardiac failure, (2) auricular fibrillation, (3) auricular thrombosis and arterial embolization, (4) subacute bacterial endocarditis, (5) bronchopulmonary infections, (6) laryngeal nerve paralysis, (7) dysphagia. In later years mitral stenosis may be complicated by hypertension and coronary arteriosclerosis.

Rokitansky[92] first stressed that pulmonary tuberculosis is very uncommon in cases of mitral stenosis because of the protective action of pulmonary congestion, but this classic belief has been repeatedly questioned.[15, 29]

Diagnosis

The diagnosis of mitral stenosis depends on recognition of the characteristic diastolic-presystolic murmur in association with roentgen ray evidence of a large left atrium or a mitralized heart. If the murmur is typical, the diagnosis is justified even if there is no demonstrable enlargement of the left atrium. The diagnosis is supported by a history of rheumatic fever or by fluoroscopic demonstration of calcium in the mitral valve cusps. It should be reemphasized that the typical presystolic murmur may be absent if there is auricular fibrillation or a huge, dilated left atrium. But the apical diastolic murmur persists. Other diagnostic signs suggesting mitral stenosis are the sharp, snappy first sound at the apex, the "opening mitral snap" following the second sound at the apex and a diastolic thrill. Electrocardiographic records showing right axis deviation, large, notched P waves and auricular fibrillation also suggest mitral stenosis, especially if there is a history of rheumatic fever.

If, in addition to the above signs, there is a systolic apical murmur and enlargement of the left ventricle, mitral insufficiency is also present.

Differential diagnosis involves determination of etiology as well as of the valvular lesion. The possibility of surgical correction may increase the importance of differentiating occasional cases of mitral stenosis due to tumors or thrombi.

A presystolic murmur, indistinguishable from that of mitral stenosis, may occur in aortic insufficiency (Austin-Flint murmur, p. 594). But this is rare

except in the presence of heart failure. If mitral stenosis is present, other physical signs such as the sharp first sound and the accentuated pulmonic second sound, and a mitralized configuration of the heart will be discovered. In aortic insufficiency there is a high-pitched soft diastolic murmur to the left of the sternum or in the aortic area; there may be peripheral phenomena of aortic insufficiency, and roentgenologic examination shows a boot-shaped cardiac contour due to enlargement of the left ventricle.

The differentiation of the Graham Steell murmur of mitral stenosis from the diastolic murmur of aortic insufficiency has been noted. The crescendo murmur and/or the sharp first sound of mitral stenosis may be simulated in asthenic individuals with tachycardias of various origins, in persons with Graves' disease or with cardiac neurosis. The auricular sounds in cases of 2:1 heart block may simulate a diastolic rumble. Splitting of the first sound or audibility of the auricular sound may be mistaken for the low pitched presystolic murmur of mitral stenosis, but the duration is much less than that of a true murmur. An apical mid-diastolic murmur in the absence of mitral stenosis may be heard in early rheumatic fever and disappear later.[17] Duplication of the second sound in young recruits has been described as simulating the signs of mitral stenosis.[21] The pulmonic second sound is accentuated in children and young adults.

The physician may mistakenly interpret the various pulmonary symptoms and signs as indicating pulmonary tuberculosis or he may make a diagnosis of bronchopneumonia without recognizing the underlying valvular disease or complicating pulmonary embolization. Paralysis of the left recurrent nerve may suggest the diagnosis of syphilitic thoracic aneurysm or bronchogenic carcinoma. The observation of large hilar shadows due to the dilated pulmonary vessels in mitral stenosis with pulmonary hypertension has led to x-ray therapy for lymphosarcoma and to operative intervention for neoplasm.

PROGNOSIS AND TREATMENT OF MITRAL VALVE DISEASE

Since mitral disease is essentially a consequence of rheumatic fever, its prognosis and treatment has been discussed with rheumatic heart disease (page 750). While some statistical studies indicate that the type of valvular disease is not significant for prognosis, others suggest that the outlook in mitral disease, especially mitral stenosis, is less favorable than in aortic valvular lesions of rheumatic origin. The average age at death varies between thirty and forty-five years, but about 20 to 25 per cent survive the age of fifty.[8] Many individuals live a practically normal life span, and engage in normal activities. Most women with compensated mitral stenosis are able to bear one or more children without serious consequences. However, pregnancy in a person with mitral stenosis is occasionally complicated by the onset of cardiac failure or subacute bacterial endocarditis, and rarely by acute pulmonary edema or a dangerous form of chorea.

Persistence of rheumatic activity warrants an unfavorable prognosis. The prognosis is generally worse the larger the size of the heart, since the heart size usually reflects the severity of myocardial damage and the degree of cardiac failure. Persistent auricular fibrillation is usually an end stage, with death apt to follow in one to three years. Left-sided failure with pulmonary congestion may be present for many years, but the outlook is not as good as for patients who are perfectly compensated. Right heart failure is a serious omen, but death does not ensue as rapidly as with right heart failure in aortic valve disease. Many patients live for three to five years or more after its onset, if proper

treatment is employed. Embolization is almost always an unfavorable omen, especially since it is frequently associated with heart failure and auricular fibrillation. Once embolization occurs, it is usually recurrent. Rarely, patients live for five years or more after an embolus in mitral stenosis. Associated valvular disease usually enhances the seriousness of the condition because the more valves involved, the more serious is the myocardial injury apt to be. Statistical observations are in disagreement on this point. Associated cardiac disease, such as coronary arteriosclerosis, also diminishes life expectancy, but clinical coronary disease usually occurs in patients who have already survived a relatively long time.

The cause of death is cardiac in 70 to 90 per cent of cases. Stone and Feil[109] found that 81 per cent died of circulatory failure. Acute rheumatic carditis and bronchopulmonary infections are frequent causes of death, either directly or by contributing to the development or persistence of cardiac failure. Pulmonary, cerebral or visceral emboli often play an accessory or primary role in causing death. Subacute and acute bacterial endocarditis occur less frequently than in aortic insufficiency.

Favorable factors in prognosis are: absence of rheumatic activity, survival beyond adolescence, absence of symptoms and signs of either left or right heart failure, little or no demonstrable cardiac enlargement, and favorable economic and social status which permits the avoidance of undue physical and mental stress or climatic hazards and an intelligent attention to the laws of good hygiene.

The *treatment* of mitral valve disease is usually that of inactive rheumatic fever, for which the reader is referred to page 764. The possibility of surgical removal of a right atrial myxoma should be considered. Mahaim[76] has suggested that in cases of mitral stenosis the circulatory status may be improved by creation of an artificial atrial septal defect.[16a] This is based on the relatively favorable course of many congenital cases of interatrial septal defect and mitral stenosis. The additional path of egress of left atrial blood relieves the atrial and pulmonary congestion due to the mitral valvular obstruction. Harken and his associates[56] have improved the technic of mitral valvuloplasty for severe mitral stenosis and have reported a successful case. The valve was approached directly through the left atrium or pulmonary vein and the posterior cusp was resected. The objective was to produce only moderate insufficiency since gross traumatic (surgical) insufficiency is as badly supported as advanced mitral stenosis. They recommended mitral valvuloplasty for severe cases with low, fixed cardiac output, artificial interatrial shunt for those with normal output, and cardiac denervation (bilateral inferior cervical and upper dorsal—D1 to D4—sympathectomy) for cases with uncontrollable tachycardia, with or without anginal pain. More recently Bailey and associates[6a] reported pronounced relief of mitral stenosis with improved valve function after incision of the valve commissures sufficient to divide the scarred tissue and enter normal valvular tissue. The left auricular appendix has been resected for recurrent embolism.[119a]

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27

AORTIC INSUFFICIENCY

ETIOLOGY AND PATHOLOGY

Insufficiency of the aortic valve is due almost exclusively to rheumatic fever or syphilis. Occasionally aortic insufficiency may result from bacterial endocarditis or from trauma.[26] It may be associated with pronounced hypertension[19] and aortic arteriosclerosis, or dissecting aneurysm of the aorta.[48] The relative incidence of rheumatic and syphilitic aortic insufficiency depends chiefly on the varying geographical incidence of rheumatic fever and syphilis. Aortic insufficiency in patients below the age of thirty-five is almost always rheumatic. Uncomplicated rheumatic aortic insufficiency may occur but it is usually combined with mitral valvular disease.[11] Aortic insufficiency occurs predominantly in males in contrast with the predominance of mitral stenosis in females.

Rheumatic Aortic Insufficiency. Rheumatic fever invades the aortic valve by way of the aortic valve rings. The valve becomes thickened by edema, inflammatory cells and granulation tissue. Verrucae develop at the line of closure as a result of the extrusion of degenerated inflamed superficial valvular tissue and the secondary deposition of thrombotic material from the blood stream. The inflammatory exudate becomes organized and scar tissue is formed which subsequently contracts. The cusps become stiff, thickened and deformed. They are shortened and their free margins are thickened, rolled and often inverted toward the sinus pocket. These alterations become more advanced with recurrent attacks of rheumatic fever and secondary degenerative changes including atheroma and calcification.

The valve becomes insufficient because: (1) the shortened cusps are too small to close the normal aortic orifice; (2) the deformity and rigidity of the cusps prevents their proper coaptation. *Subsequently aortic stenosis may be associated or may become the predominant lesion.*

Syphilitic Aortic Insufficiency. The cardiac and aortic lesions of syphilis will be described in detail (p. 817). The *aortic valve* is affected by extension of the aortic syphilitic inflammatory tissue to the valve cusps. Unlike the rheumatic lesions, syphilis hardly ever attacks the valve cusps directly, but confines its mischief to the aortic valve commissures (syphilitic commissural valvulitis). Aortic insufficiency in syphilis may be due to three factors: (1) widening of the commissures, (2) shortening of the cusps so they cannot reach each other to occlude the orifice, and (3) dilatation of the aortic orifice concomitant with dilatation of the ascending aorta. Since the cusps become separated, not ad-

herent as in rheumatic fever, aortic stenosis does not develop. However, I have in occasional instances seen calcific aortic stenosis in hearts with syphilitic aortic insufficiency, and similar cases have been reported.

Aortic Insufficiency in Bacterial Endocarditis. Aortic insufficiency in cases of subacute or acute bacterial endocarditis is usually the result of a previous rheumatic inflammation. Occasionally, however, the bacterial vegetations may erode the valve substance and either produce an aneurysm of the cusp or perforate it. Thus a previously normal valve may become insufficient or a previous insufficiency may be intensified. Furthermore the valvular vegetations themselves, if large, may prevent perfect apposition of the cusps and closure of the aortic orifice.

Traumatic Aortic Insufficiency. Aortic insufficiency results rarely from trauma. In 1928 Howard [29] collected from the literature 113 cases of valvular disease due to trauma, most of which were unproven. The aortic valve is more often injured than any other valve. The injury may result from the *strain* of an unusually strenuous muscular effort or from *direct trauma* caused by a blow to the chest wall or a fall from a height. Rupture of the aortic valve by contrecoup as a result of a blow to the chest wall was demonstrated experimentally by Barié[2] on cadavers. The injury is presumed to occur when the ventricles are in early diastole and the aortic valves under maximum tension. Traumatic aortic insufficiency is encountered almost exclusively in males.

Pathologic examination usually reveals a linear tear of a valve cusp. More than one cusp may be affected. Not infrequently the valve injury is part of an extensive tear involving the root of the aorta. In instances of muscular strain the cusp is more apt to be torn at its attachment to the aorta; in instances of trauma it is usually torn through its free margin.[45] The ruptured valve or aorta is generally the seat of preceding disease especially syphilis or bacterial endocarditis. Occasionally a normal valve may be ruptured as in the case recently reported by Kissane, Koons and Fidler (p. 989).

Arteriosclerosis and Hypertension (Functional Aortic Insufficiency).[33, 23] I have occasionally observed clinical evidence of aortic insufficiency in patients with pronounced arteriosclerotic dilatation of the aorta and hypertension, whose aortic valves were normal at postmortem examination. Garvin[19] found 14 such cases among 200 consecutive cases of hypertensive heart disease studied at autopsy.

Dissecting Aneurysm. In occasional cases of dissecting aneurysm of the aorta, the dissection may involve the attachment of the aortic cusps, or the aneurysm may interfere with their closure.

PATHOLOGIC PHYSIOLOGY

Volume and Effects of the Reflux. The dynamic effects of aortic insufficiency are due to a significant regurgitation of blood from the aorta into the left ventricle.[50] Allan[1] observed in artificial circulation experiments that large refluxes were obtained with leaks equal to one half to one seventh of the area of the aortic orifice. Wiggers and Maltby[54] determined that the amount of the reflux depended essentially on the size of the leak; the larger the leak, the larger the reflux. The quantity of reflux may amount to more than 50 per cent of the systolic discharge.[54, 38] With large leaks, most of the regurgitation occurs in the early part of diastole before the mitral valve is open so that there is little interference with the inflow of blood from the left atrium. In small leaks,

most of the regurgitation takes places late in diastole after the opening of the mitral valve. But the magnitude of the reflux with small leaks is too slight to affect significantly the entrance of blood from the left atrium. Thus neither with small nor large leaks is there a rise in intraatrial pressure.

Cardiac Compensations for the Aortic Reflux. Despite the large reflux, a relatively normal cardiac output is maintained by: (1) a more forceful contraction of the left ventricle; (2) a prolongation of the period of systolic ejection.

1. The addition of the aortic reflux to the normal inflow from the left atrium increases the diastolic volume of the left ventricle and its initial intraventricular tension. According to Starling's Law of the Heart, this results in a more powerful contraction of the left ventricle and a greater ejection of blood in systole.

2. In experimental and clinical aortic insufficiency the phase of isometric contraction is shortened, while the period of systolic ejection is prolonged to the same degree. Thus in addition to the higher pressure attained, the left ventricle has a longer period of ejection in which to expel its increased diastolic volume. The diminished aortic diastolic pressure against which the ventricle ejects its stream is an additional compensatory aid. In animal experiments, an increased cardiac rate also helps to maintain a normal cardiac output, but this factor does not usually operate in human aortic insufficiency in the absence of heart failure.

Effect of Aortic Insufficiency on Cardiac Size. The increased diastolic blood volume and intraventricular tension in the left ventricle lead to enlargement of that chamber. Rosenbach,[46] who first produced aortic insufficiency in rabbits, noted an initial dilatation followed by hypertrophy of the left ventricle. Other observers have also repeatedly demonstrated cardiac hypertrophy in animals following experimental aortic insufficiency.[17, 3, 27]

In human aortic insufficiency, dilatation and hypertrophy of the left ventricle are invariably found in cases with significant regurgitation. The hearts in human aortic insufficiency are the largest encountered in cardiac pathology. They are the so-called ox-hearts or cor bovinum of classical literature. The weight generally exceeds 500 gm., often 750 gm. and occasionally even 1000 gm. The enlargement involves chiefly the outflow tract (the anterior half of the left ventricle and interventricular septum), which becomes greatly elongated and hypertrophied. The endocardium in this region is often whitened and thickened, and there may be crescentic thickenings or pockets ("birds'-nests") resembling secondary valve structures, below the aortic valve. These endocardial changes are mute evidence of the tension of the regurgitant stream.

CLINICAL FEATURES

Stage of Compensation

Whereas in mitral stenosis *perfect* compensation for a long span of years is the exception, in aortic valvular disease it is the rule. In mitral disease, the limited compensatory power of the weak left atrium and the absence of an efficient valve between it and the pulmonary veins permit some degree of pulmonary congestion (and exertional dyspnea) early in the disease. In aortic valvular disease, the strong left ventricle and the efficient mitral valve may long prevent any stasis in the pulmonary circuit.

In the absence of complications, patients with pure or predominant aortic insufficiency often live many years or even a normal life span, either without

knowledge of their disease or without significant disturbance. I have known a number of such individuals who engaged actively in strenuous sports or in occupations involving hard physical labor.

Occasionally, even with almost perfect compensation, there are subjective disturbances due either to local cardiac compensations or to the peripheral changes in vascular dynamics. The enlarged heart with its forceful precordial heave may be very discomforting to the patient, especially on lying down. Lying on the left side must usually be avoided. He may be greatly disturbed by the audible beat of his heart and cervical vessels as he rests against the pillow. There is sometimes an uncomfortable ticking in the throat due to vascular pulsation of the uvula. Sleep may be disturbed by these sensations or by terrifying dreams. The latter usually occur when there is some degree of cardiac failure. Generally the patient, if compensated, becomes adjusted to the various pulsations and his sleep is little if at all disturbed. *Dizziness,* particularly with sudden change of position, is not rare and is probably due to transient cerebral anemia caused by rapid, severe changes in pressure in the cerebral vessels.

Certain symptoms encountered in aortic insufficiency are not due to the valvular disease itself but to associated lesions. When due to rheumatic heart disease, aortic insufficiency is usually combined with mitral disease and not infrequently with aortic stenosis. These may modify the clinical picture. When aortic insufficiency is due to syphilis, luetic narrowing of the coronary arteries is generally associated and aortic aneurysm may occur. In patients beyond middle age with either rheumatic or syphilitic aortic insufficiency, there is frequently an associated arteriosclerosis of the coronary arteries. It is even possible that this occurs prematurely because of vascular damage due to rheumatic fever or syphilis. *Paroxysmal dyspnea* which Longcope[40] emphasized as a frequent manifestation of luetic aortic insufficiency is generally due to left ventricular failure and is not a symptom of the compensated stage. *Cardiac pain,* also described as a typical feature of luetic aortic insufficiency, is usually not due to the valvular lesion as such. Its occurrence is of sufficient interest to merit special discussion.

Cardiac Pain in Aortic Insufficiency

Angina pectoris has long been regarded as a symptom of aortic insufficiency, but it is rarely due to the uncomplicated valvular lesion itself. In the cases of syphilitic origin, the cardiac pain is usually due to the frequently associated stenosis of the coronary ostia and not infrequently to concomitant coronary arteriosclerosis. Angina pectoris is very uncommon in uncomplicated rheumatic aortic insufficiency, but in older persons it may occur because of coronary arteriosclerosis or because superimposed calcification of the aortic valve leads to stenosis.

However Schwartz,[47] and later Lewis,[37] and others[16, 36] reported a distinct form of angina pectoris in cases of rheumatic aortic insufficiency, occurring in severe paroxysms, usually at night. The attacks were accompanied by a rise in blood pressure, increased pulse and respiratory rate, palpitations and by vasomotor disturbances such as flushing and sweating. The pain occurred at rest but sometimes was precipitated by excitement. It was often relieved by nitroglycerin. But I have seen one patient with this syndrome who had such severe and persistent pain that he took 25 or more tablets of nitroglycerin (each 1/100 grain) daily to obtain relief.

Cardiac pain in uncomplicated (rheumatic) aortic insufficiency has been attributed to: (1) diminished coronary flow because of a low diastolic pressure and (2) increased demand for blood because of the increased weight and work of the hypertrophied heart. But this explanation does not completely explain all the facts. Thus it is not clear why so many patients with rheumatic aortic insufficiency and an extremely low diastolic pressure fail to have angina pectoris. Laplace[31] denied the significance of the low diastolic pressure in the production of cardiac pain in aortic insufficiency because this symptom was less frequent in a group of patients with extremely low diastolic pressure than in the group with moderately low diastolic pressure. Finally it is uncertain whether the coronary blood flow is actually diminished in aortic insufficiency despite the low diastolic pressure. Thus, Green[24] found that the minute coronary flow was increased because the improved flow during systole more than compensated for the reduction during diastole. By catheterizing the coronary sinus in patients with aortic insufficiency, Bing et al.[4a] found the coronary blood flow and cardiac oxygen consumption increased.

Left Ventricular Failure in Aortic Insufficiency

Failure of the left ventricle in aortic insufficiency usually occurs after a relatively long period of perfect or nearly perfect compensation. The left heart failure of aortic insufficiency differs in some respects from that of mitral stenosis because in the former it is the left ventricle, in the latter the left atrium that gives way. Because of the greater strength of the left ventricle as compared with that of the left atrium, a longer period elapses before left heart failure occurs in aortic insufficiency than in mitral stenosis.

Heart failure is often the result of recurrent rheumatic infection in a heart with rheumatic aortic insufficiency and of progressive coronary ostial narrowing in a heart with the syphilitic variety. In both forms of aortic insufficiency, increasing fatigue of the greatly enlarged heart, associated degenerative disease of the coronary arteries, intercurrent infections, etc., may contribute to the development of heart failure. Left ventricular failure is associated with dilatation of that chamber and of the mitral orifice with consequent functional mitral insufficiency. The dilatation of the left atrium which follows is inadequate to compensate effectively for the regurgitation due to the sudden failure of the left ventricle and mitral incompetence. In mitral stenosis, the compensatory effect of a dilating left atrium develops more gradually, concomitant with progressive deformity of the valve, and is therefore more thorough. For the same reason, the engorgement of the pulmonary circulation in aortic insufficiency occurs too rapidly to permit accommodation, and the clinical manifestations of pulmonary stasis are more intense than in organic mitral disease.

Dyspnea on exertion is the earliest signal of left heart failure in aortic insufficiency, as it is also of mitral stenosis. This is slight at first, but becomes rapidly and progressively worse. Long periods of dyspnea on exertion without other symptoms of failure may occur occasionally, but usually other, severer symptoms are soon associated. An outstanding and characteristic symptom of left heart failure in aortic insufficiency is a most distressing form of *paroxysmal dyspnea.* It appears in sudden attacks, lasting up to fifteen minutes, sometimes after exertion, but much more often while the patient is at rest, especially while asleep. Paroxysmal dyspnea is especially characteristic of luetic aortic disease as depicted in Longcope's vivid description.[40] It also occurs with

rheumatic aortic insufficiency but is much less common than with the syphilitic type. The difference in incidence may be due on the one hand to the frequent narrowing of the coronary ostia in syphilitic disease and on the other to the modifying effect of associated mitral defects in rheumatic aortic insufficiency.

Orthopnea sooner or later is added to the above-mentioned symptoms.

In cases of aortic insufficiency due neither to rheumatic fever nor syphilis, symptoms of left heart failure may be absent or overshadowed by other features of the causative disease. In *subacute bacterial endocarditis,* the valvular lesion may be indicated only by a change in character of the aortic murmur or by the fresh development of an aortic diastolic murmur. In *arteriosclerotic* aortic insufficiency, there may be no clinical evidences of the lesion except the murmur. In the uncommon cases of *traumatic aortic* insufficiency, the lesion may be denoted by the murmur alone without associated symptoms, by the gradual development of heart failure or rarely by an acute fulminating left ventricular failure with pulmonary edema and death.

Right Heart Failure in Aortic Insufficiency

The symptoms of left heart failure in aortic insufficiency are eventually combined with or overshadowed by those of failure of the right ventricle. The agony of severe paroxysmal dyspnea is sometimes relieved when the right heart fails and diminishes the forward pressure and engorgement in the lungs. The right ventricle dilates, the tricuspid valve becomes insufficient and the right atrium is enlarged by reflux and stasis. The venous pressure in the venae cavae and peripheral veins rises. As a result the neck veins and those on the extremities appear engorged, the liver becomes enlarged, palpable and tender, and peripheral edema is observed. Ascites may be somewhat less common than in mitral stenosis but hydrothorax is frequent.

Objective Evidences of Aortic Insufficiency

Cardiac Signs. *Inspection and Palpation.* The apical impulse is heaving and located to the left of and below its normal site. Occasionally it is seen or felt far out in the left axilla or as low as the sixth or seventh interspace. Sometimes there is a diffuse systolic *depression* of the anterior chest wall, medial to the forceful apical thrust. This depression is caused by the aspirating effect of the contracting ventricle on the chest wall, as its large volume of blood is expelled into the arterial tree.[14] A diastolic pulsation of the chest wall is due to the filling of the left ventricle.

Percussion may disclose the enlargement of the left ventricle, but this is best demonstrated by roentgenologic examination.

Auscultation. The characteristic sign is a soft, high-pitched *diastolic murmur,* likened to the sound made by the pouring of water. In luetic aortic insufficiency it is often louder and lower-pitched than in the rheumatic form of the disease. In cases of traumatic etiology, the murmur is often extremely loud and musical in quality,[4] or it may resemble the cooing of a dove or the call of the seagull (seagull murmur).[10] In cases due to extreme physical exertion the murmur may be audible without applying the stethoscope or the ear to the chest.

The diastolic murmur starts immediately after the second sound. Occasionally the second aortic sound is absent. The murmur is best heard in the second right intercostal space or along the left border of the sternum in the third or fourth

interspace. Occasionally the murmur has been described as being loudest in the pulmonic area, and rarely near the apex or left axilla. In my experience, the diastolic murmur of rheumatic aortic insufficiency is usually best heard along the left border of the sternum, while that due to luetic disease is best heard either in this location or in the second right interspace.

The high pitch and soft quality of the diastolic murmur of aortic insufficiency make it one of the most difficult to hear, and one about whose presence in a given case there is most disagreement. Thrills are rarely associated because of the high frequency of the murmur. The murmur may often be more readily discovered with the naked ear or a straight, wooden monaural stethoscope. I have heard the murmur most readily with the Bowles type of stethoscope. Recognition is enhanced if the patient is examined while standing or sitting, and bending slightly forward. Elevating the arms and holding the breath in expiration also help.

A *systolic* murmur over the base of the heart often accompanies the diastolic murmur of uncomplicated aortic insufficiency. It may be high pitched and blowing or harsh and loud. The combined systolic and diastolic aortic murmurs produce the characteristic "bellows murmur." In Corrigan's[12] original description of aortic insufficiency, the aortic systolic blowing murmur and its propagation into the carotid and subclavian arteries were described as characteristic of the disease. In my experience, this systolic murmur usually occurs in the luetic cases, and is present in rheumatic aortic insufficiency only when there is considerable stenosis. The systolic murmur is probably due to concomitant dilatation and changes in the wall of the adjacent aorta; it may therefore represent a functional (relative) aortic valvular stenosis.

An *apical systolic murmur,* independent of that in the aortic region, may also be present when the left ventricle fails, becomes dilated and produces a accentuated due to increased pressure in the pulmonary circulation.
relative mitral insufficiency. The second pulmonic sound may then become

The Austin Flint Murmur in Aortic Insufficiency. Occasionally there is a low, rumbling, late diastolic or presystolic apical murmur in aortic insufficiency, which is indistinguishable from the characteristic murmur of mitral stenosis. This murmur, in a case of aortic insufficiency without organic mitral stenosis, has been termed the Austin Flint murmur, after the man who first described it.[18] It may be associated with a diastolic thrill. My experience conforms with the observation of Laubry and Pezzi[34] that the Austin Flint murmur is generally heard when there is left ventricular failure. The frequency of the murmur has been variously estimated, but in routine clinical practice it is encountered only occasionally. On the other hand, Thayer[51] noted that the Austin Flint murmur had been present at one time or another in 43 per cent of 74 hearts with aortic insufficiency, proven at autopsy to have normal mitral valves.

The explanation of the Austin Flint murmur is still disputed. The aortic regurgitant stream may force the anterior (aortic) mitral leaflet (which is nearest the aortic valve) upward, thus producing a functional mitral stenosis impeding the inflow of blood from the left atrium.[25] This explanation is supported by the clinical and experimental observations of Herrmann[27] who found that the Austin Flint murmur occurred when the posterior aortic cusp was incompetent. This is the leaflet nearest the anterior mitral cusp, and the one whose insufficiency would most readily permit a regurgitant stream to strike the anterior mitral cusp. Gouley[22] found evidence of a defect in the right

aortic cusp. The murmur occurs most frequently if left ventricular failure ensues, because of the consequent dilatation of the left atrium and its more forceful ejection of blood past the obstructed valve. With digitalization or relief of failure by other therapeutic methods, the Austin Flint murmur may disappear. This disappearance after relief of failure confirms the interpretation that the murmur was of the Austin Flint type. According to the phonocardiographic observations of Luisada[42] the so-called Austin Flint murmur is usually either a gallop rhythm or an auditory misinterpretation of the heart sounds. In rheumatic aortic insufficiency, the diagnosis of an Austin Flint murmur is hazardous because of a frequently associated mitral stenosis which is more likely to produce a presystolic murmur. The clicking third sound and palpable tap of organic mitral stenosis do not accompany the Austin Flint murmur and when present may help as distinguishing signs.

Roentgenologic Examination of the Heart. 1. With perfect compensation and slight or early lesions, the cardiac outline may appear relatively normal, since a small degree of left ventricular enlargement is indistinguishable. With more advanced lesions, the heart assumes a characteristic *aortic configuration* (Fig. 7*A*, p. 27). The lower left cardiac contour, which in the anteroposterior view represents the left ventricle, becomes elongated and enlarged downward and to the left. The angle formed with the pulmonary artery salient is much sharper than normal. The figure of the resulting heart shadow has been described as boot-shaped, the rounded apex of the heart corresponding to the toe of the boot. The aortic knob is usually prominent and the rest of the aortic shadow may be slightly dilated. The pulsations of both the left ventricle and the aorta have an increased excursion as observed on fluoroscopic examination or on roentgenkymograms. In the left oblique (second) position, with the left shoulder rotated anteriorly toward the screen, the large left ventricle is seen, encroaching on or even extending behind the shadow of the spine (Fig. 7*B*, p. 27).

2. *With left ventricular failure,* there is a functional insufficiency of the mitral valve with secondary dilatation of the left atrium, and of the pulmonary vessels. The cardiac shadow now assumes some of the features of mitral disease which modify the aortic configuration ("mitralized aortic configuration"). The modification is more striking if mitral stenosis is associated with aortic insufficiency.

3. *When right heart failure develops,* both the right ventricle and right atrium become dilated. The total cardiac shadow appears huge, with an extremely wide transverse diameter.

The Electrocardiogram in Aortic Insufficiency. In well developed cases there is usually a pronounced left axis deviation. The major deflections are of high voltage. There may be a depression in ST_1 and an inversion of T_1, as well as corresponding changes in the precordial leads, denoting left ventricular strain (Fig. 16, p. 38). When aortic insufficiency is associated with mitral disease, variable pictures are obtained. Often there are tall, broad or notched P waves as well as left ventricular preponderance.

Peripheral Signs of Aortic Insufficiency. *1. Low Diastolic and High Pulse Pressure.* A low diastolic pressure is characteristic of aortic insufficiency. The pressure, as indicated by the change in sound over the brachial artery to a muffled tone, is usually 60 mm. Hg or lower. Often the sounds continue to be heard until the pressure in the blood pressure cuff is zero. Since the systolic

pressure is usually normal or somewhat elevated, the difference between it and the low diastolic pressure gives a pulse pressure which is usually increased. Instead of a normal of 30 to 50 mm. Hg, the pulse pressure usually exceeds 60 mm. and often reaches 100 mm. or more. In a young man of thirty with syphilitic aortic insufficiency, I observed a blood pressure of 300/38, i.e., a pulse pressure of 262 mm. Hg. The diminished diastolic pressure is the result of aortic regurgitation with consequent relative diastolic emptiness and relaxation of the arterial tree.

2. Corrigan (Radial) Pulse. Aortic insufficiency is often associated with a characteristic pulse (*Corrigan pulse*[12]) which strikes the palpating finger with a rapid, forceful jerk and quickly disappears (celer et alter). It is described as having a *waterhammer* quality because of its sudden impact, and a *collapsing* quality because it falls away so rapidly. The waterhammer impression is the consequence of the sharp rise in aortic pressure and the rapid filling of the radial artery. The collapse, which begins toward the end of systole,[49] is due to the sharp drop of pressure in both the central and peripheral arteries.[53] It has also been explained as the result of the very increased velocity head of the blood stream and the consequently rapid egress of blood from the arterial system.[21] The waterhammer effect is accentuated if the pulse is examined with the patient's arm elevated, because the radial artery is then in more direct line with the outflow stream from the aorta, and because gravity increases the blood pressure changes at the wrist. While the Corrigan pulse is characteristic of aortic insufficiency, Tice[52] having observed it in 95 per cent of 124 cases, it may occur in cases of patent ductus arteriosus, arteriovenous fistula, Graves' disease, and in severe anemia, fever and conditions associated with peripheral vasodilatation.

The *pulse wave* as seen on sphygmograms shows a sharp, almost vertical, tall upward limb, and a steep, downward stroke.

The *pulse rate* is normal in well compensated cases. In failure, a moderate tachycardia (90 to 100 per minute) is frequent.

3. Visible Arterial Pulsations. Sometimes a tentative diagnosis of aortic insufficiency can be ventured on observing marked pulsations in the neck vessels. Such visible pulsations result from the sudden systolic filling of the large collapsed arteries. Corrigan's[12] graphic description of aortic insufficiency contains a vivid picture of these visible pulsations in both carotid arteries, in the temporal arteries and in other large vessels. The forcefulness of these pulsations may impart a to and fro motion to the entire head, synchronous with the cardiac cycles (de Musset's sign). With the ophthalmoscope, one may also observe pulsation of the retinal arteries as well as of the veins. F. Muller[43] described pulsations in the uvula, Rosenbach[46] in the liver, and Gerhardt[20] in an enlarged spleen.

4. Capillary Pulsation. Quincke[44] observed an alternate paling and flushing of the skin in aortic insufficiency which he ascribed to capillary pulsation (Quincke pulse). Clinically this phenomenon may be elicited in several ways: (a) by observing the nail bed or skin at the root of the nail while pressure is made on the tip of the nail; (b) by observing the edge of the blanched region when the mucous membrane of the lip is compressed by a glass slide; (c) by observing the earlobe or fingertip while it is being transilluminated by a flashlight. Actually the phenomenon observed is due not to the pulsation of the capillaries but to that of the subpapillary arteriolar and venous plexuses which

are essentially responsible for the redness of normal skin.[7, 13] Lewis and Drury[38] attributed capillary pulse to arteriolar dilatation, but this explanation does not appear to apply to the "capillary" pulse of aortic insufficiency. The "capillary" pulse is not pathognomonic of aortic insufficiency. It may also be observed in a normal subject when the skin is warm, in a number of unrelated conditions such as fever, anemia, Graves' disease, and whenever there is local dilatation of the terminal peripheral vessels.

5. Disproportionate Femoral Systolic Hypertension (Hill's Sign). Hill and Rowlands[28] observed that the slight, physiologic excess of blood pressure in the femoral artery over that in the brachial was greatly exaggerated in aortic insufficiency.[35] Instead of the normal difference in systolic pressure amounting to 10 to 20 mm. Hg, in aortic insufficiency this difference may be 60 to 100 mm. Hg or more. Since the femoral artery is in a direct line with the aortic stream, while the brachial issues from the aorta at a right angle, the femoral artery receives not only the pressure head but also the velocity head of the aortic stream. In normals the velocity head is slight and the femoral pressure exceeds the brachial by a correspondingly small amount. But since in aortic insufficiency the velocity head is considerable, there is a pronounced excess of pressure on the femoral as compared with the brachial artery. Hill's sign is absent in cases of functional aortic insufficiency associated with hypertension.[39]

6. "Pistol-shot" Femorals. Femoral Double Tone (Traube's Sign). Femoral Murmur (Duroziez's Sign). Auscultation over the femoral artery reveals a booming sound synchronous with each pulse through the vessel. This characteristic sound has been described as resembling a pistol shot, and is probably due to vibrations of high frequency caused by the sudden elevation of pressure in the vessel.[9]

Sometimes a double sound (*Traube's double tone*[32]) is heard in aortic insufficiency instead of the single "pistol-shot." Its mechanism is uncertain.[41]

A systolic murmur is heard over the femoral artery in normal individuals if the vessel is slightly compressed by the bell of the stethoscope. This murmur is due to the vibrations set up by the rapid passage of blood past an obstruction. In aortic insufficiency, a diastolic as well as systolic murmur is audible over the compressed vessel, because there is a rapid diastolic regurgitation toward the heart as well as systolic forward passage toward the periphery. This characteristic double murmur, termed *Duroziez's sign,*[15] was encountered in 88 per cent of Tice's[52] 124 cases of aortic insufficiency. Like capillary pulsation, it is not a pathognomonic sign and is observed in other conditions with a rapid peripheral blood flow or vascular dilatation, such as Graves' disease, febrile states, anemia, and on warming the lower extremity. But the pathogenesis of the murmurs in these conditions is different.[6]

The above peripheral signs of aortic insufficiency are probably present only when there is a large leak with significant regurgitation. Lewis[37] has applied the term *"free aortic regurgitation"* to those cases in which these signs are observed.

Complications

Cardiac failure is the most frequent complication of aortic insufficiency. It is almost an integral part of the course of the disease, because there are few or no significant symptoms before failure develops. A *reactivation of rheumatic fever* is a serious complication which often precipitates cardiac failure. *Sub-*

acute bacterial endocarditis frequently complicates aortic insufficiency, usually while the lesion is still well compensated. When the complication occurs, the underlying aortic insufficiency is almost always rheumatic. In luetic aortic insufficiency, *narrowing of the coronary ostia* is generally associated. This produces an *anginal syndrome,* cardiac failure, and often sudden death. Bronchial and pulmonary infections and embolization may complicate aortic insufficiency but rarely in comparison with their occurrence in mitral stenosis. Auricular fibrillation and other arrhythmias are relatively uncommon.

DIAGNOSIS

The diagnostic features of aortic insufficiency are: (1) a *high-pitched diastolic murmur* over the aortic area or along the left border of the sternum or occasionally in the cardiac apical region; (2) *enlargement of the left ventricle,* especially as indicated by the characteristic boot-shaped cardiac shadow seen roentgenologically; (3) *distinctive peripheral circulatory phenomena,* such as the high pulse pressure and low diastolic pressure, the collapsing (Corrigan) pulse, visible arterial pulsations, capillary pulse, femoral pistol-shot and Duroziez's sign.

The characteristic diastolic murmur is in itself sufficient to justify the diagnosis; on the other hand a diagnosis of aortic insufficiency should rarely be made in the absence of the murmur even when the other clinical features are present. Sometimes the roentgenologic findings of left ventricular enlargement and pronounced aortic pulsations, or the peripheral circulatory findings, first suggest the diagnosis, but the latter is proved by the subsequent discovery of the diastolic murmur.

The diastolic murmur of aortic insufficiency may have to be distinguished from the rare Graham Steell murmur of pulmonic insufficiency. The latter should be diagnosed only in the presence of mitral stenosis or pulmonary disease sufficient to produce significant right ventricular strain. The peripheral phenomena of aortic insufficiency do not accompany the Graham Steell murmur, the cardiac shadow shows right, not left ventricular enlargement and the aorta is not prominent and conspicuously pulsatile.

The *etiologic diagnosis* usually involves distinction between rheumatic and syphilitic aortic insufficiency.[30] The history of rheumatic fever or syphilis, the knowledge of the duration of the murmur, and serologic study may be helpful. The association of mitral stenosis suggests that the aortic insufficiency is rheumatic. The presence of a loud aortic systolic murmur and a diastolic murmur which is most audible in the second right interspace usually denote a syphilitic etiology for the aortic insufficiency. A very soft high-pitched diastolic murmur along the left border of the sternum is usually of rheumatic origin.

Traumatic insufficiency is suggested by a history of unusual physical exertion or penetrating or nonpenetrating injury to the chest followed by a loud, musical murmur (seagull murmur).

Aortic insufficiency may be attributed to a bacterial endocarditis if an aortic diastolic murmur first appears during the course of the disease. Frequently this denotes a preexistent bicuspid aortic valve.[8]

PROGNOSIS AND TREATMENT

The prognosis and treatment are discussed in detail in the chapters on rheumatic fever, syphilis, bacterial endocarditis and congestive heart failure.

In general the prognosis in cases of *syphilitic aortic insufficiency* is much less

favorable than in the rheumatic cases. Sudden death is common in the syphilitic cases due to associated coronary ostial involvement. Sometimes specific antiluetic therapy relieves the chest pain; it probably prolongs life (p. 828). Adequate early treatment of uncomplicated syphilis is more important, for it prevents the occurrence of the cardiovalvular complication.

In the *rheumatic cases* the outlook is favorable once rheumatic fever becomes inactive. Satisfactory treatment of bacterial endocarditis has greatly reduced the hazard from this complication. In the uncommon instances of severe angina pectoris associated with rheumatic aortic insufficiency, alcohol injection of the sympathetic rami communicantes of the upper four thoracic segments may relieve the pain.[5]

ARTERIOVENOUS FISTULA

Arteriovenous fistula[76, 84, 85, 88, 74] denotes a direct communication between an artery and vein, often with the formation of an aneurysmal sac. This subject is included in this volume because the lesion imposes a strain on the heart and may induce heart failure. Because its circulatory dynamics are similar to those of aortic insufficiency, they are discussed in this chapter. There are also many similarities to patency of the ductus arteriosus, which may be viewed as a form of congenital arteriovenous fistula.

Etiology and Pathology

Arteriovenous fistula may be acquired or congenital. The commonest cause is *trauma.* A stab, gunshot or shrapnel wound, often appearing small externally, perforates an artery and vein which are in close proximity and often in the same sheath. The femoral or iliac vessels in the thigh and the carotid artery and internal jugular vein in the neck[56] are most often affected. Rupture of a syphilitic aortic aneurysm into the superior vena cava, pulmonary artery, right atrium or ventricle produces many of the features of an arteriovenous fistula.

The involved artery becomes dilated for a long distance proximal to the fistula and its wall becomes thinned. Rarely it may become so atrophied that an aneurysm forms and may rupture. The vein becomes dilated locally due to increased pressure. Its wall may become as thick as that of an artery.[72] A local aneurysmal sac often forms and may pulsate. Varicose veins may appear locally. A collateral circulation gradually develops to supply the area distal to the fistula.

Pathologic Physiology

The circulatory disturbances are due to a shunt of 20 to 50 per cent of the cardiac output from a large artery to a large vein.

The *cardiac output* is increased, due both to an enhanced stroke output and accelerated heart rate.[69, 65] The tachycardia has been attributed to a Bainbridge reflex due to an increased venous return or to an increased right atrial pressure.[60]

The *blood volume* is usually augmented,[78, 74, 65] especially with the development of heart failure. The *circulation time* is diminished because of the short circuit of blood. The combination of accelerated speed of circulation and enlarged blood volume is responsible for an increased venous return which is translated into an augmented cardiac output.

The *systemic venous pressure* is normal in the absence of heart failure. But Cohen and associates[61] observed a moderate increase in right atrial pressure as determined by intracardiac catheterization.

Arterial blood pressure (see below).

Closure of the fistula diminishes the cardiac rate, the cardiac output and the blood volume and elevates the blood pressure by eliminating the region of diminished resistance.

Clinical Features

The diagnostic feature is a machinery-like *continuous bruit* or murmur, with slight systolic accentuation, heard over the site of the fistula. It is usually accompanied by a *thrill.*

At the site of the fistula there may be a pulsating aneurysmal mass. The superficial veins are often dilated and tortuous. The affected vein proximal to the fistula has an elevated pressure and an abnormally high content of oxygen due to the arterial shunt.[58, 66] Chronic venous insufficiency due to venous hypertension may lead to varices, stasis pigmentation and ulceration.

There may be ischemia of the part distal to the fistula and occasionally gangrene results. Eventually the development of a collateral circulation and the elevated cardiac output provide more than the normal blood flow. Consequently the affected extremity may have a higher skin temperature than the normal one and may grow longer if the fistula develops before growth is completed.

The *blood pressure:* A high pulse pressure is present due to a significant fall in the diastolic pressure with little or no change in the systolic. The waterhammer pulse and other peripheral circulatory phenomena observed in cases of aortic insufficiency may also occur with arteriovenous fistula.

The *pulse rate* is usually increased. But especially characteristic is the slowing of this rate (bradycardiac reaction) on compression or excision of the fistula, the so-called Branham's sign.[57] Following atropinization this slowing does not occur.[79]

Cardiac enlargement is usual. With small fistulas it may be demonstrable only by comparison of the size of the heart before and after excision.[86] The extent of cardiac enlargement varies with increasing size of the fistula, with the size of the feeding artery, with the duration of the fistula, and perhaps to a slight degree with the proximity to the heart.

Cardiac enlargement is dependent on the increased venous return and consequently on the increased stroke output of the heart. With increasing venous return there is an increased diastolic volume and increased diastolic tension which result in dilatation and hypertrophy (Chapter 2). It is improbable[80] that a diminished coronary blood flow accounts for cardiac enlargement, as Lewis and Drury[81] suggested. The reversibility of cardiac enlargement following cure of the fistula has suggested that most of the enlargement is due to dilatation. However it is probable that there is a significant degree of hypertrophy and that this is also reversible.[63]

Cardiac failure eventually develops in longstanding cases of large arteriovenous fistula.[73] In several such cases which I observed, it appeared probable that coronary insufficiency due to arteriosclerosis contributed to the failure of a heart enlarged by an arteriovenous fistula.

Complications. These include congestive heart failure, ulceration or gangrene of an extremity, and rarely bacterial endarteritis[62] or aneurysm or rupture of the proximal part of the artery supplying the fistula.

Congenital Arteriovenous Fistula.[93] This arises from embryonic communications between arteries and veins which fail to close.[89] The extremities, intracranial vessels, and the face and neck may be affected. In recent years congenital

arteriovenous aneurysm of the lung has aroused special interest (infra). The communications in congenital arteriovenous fistulas are more often multiple and more extensive than in the acquired cases. Varicose veins, ulceration, increased growth of an extremity are also more frequent in the former. Increased sweating and growth of hair near the fistula occur frequently. Congenital hemangiomata are often associated. On the other hand bruits are less common and the bradycardiac response less pronounced in the congenital cases.

Congenital arteriovenous aneurysm or varix of the lung[91] (cavernous hemangioma) is usually encountered among young adult males. Heredity may play a role, and there was a recent report of the condition in two brothers.[68] There may be a familial history of telangiectasia. It is characterized clinically by persistent cyanosis, polycythemia and clubbing of the fingers and toes, by exertional dyspnea, hemoptysis, chest pain, syncopal or epileptiform seizures and occasionally by focal cerebral manifestations.[59] The clinical picture resembles and is mistaken for that of cyanotic congenital heart disease or of advanced chronic pulmonary disease with cyanosis.

The heart does not usually become enlarged as in acquired arteriovenous fistula. In the case studied by Maier et al.[83] the cardiac output was essentially normal and there was no important change in circulatory dynamics. A bruit may be heard over the chest wall overlying the fistula. Hemangiomata of the skin or mucous membranes are commonly associated. Fluoroscopic examination may disclose one or multiple nodular, lobulated densities, with branches into the pulmonary vascular markings. The densities become larger during the Valsalva, and smaller during the Müller experiment.[82] They may or may not pulsate. Hilar pulsations may be seen on the side of the aneurysms. Angiocardiography may be helpful in the differential diagnosis.[91, 92] Cure may be effected by resection of the aneurysms, lobectomy or pneumonectomy.[70, 77, 59, 94]

Diagnosis

The *diagnosis*[87] depends on the finding of the characteristic bruit over the fistula. It is confirmed if the bruit disappears and the heart slows on compression of the artery proximal to the fistula. Arteriovenous fistula should be sought whenever unilateral veins or signs of venous insufficiency are found following an injury or when one limb is warmer or longer than the other. Arteriography may be helpful in diagnosis.[75, 95]

Treatment

Treatment of acquired arteriovenous fistula is essential to avoid cardiac strain and failure as well as the other complications listed. Even when frank heart failure is present, correction of the fistula usually causes a dramatic restoration of normal circulation as well as a reduction in cardiac enlargement. It is important to permit sufficient time to elapse for the development of an adequate collateral circulation before operation and to preserve this collateral circulation at operation.[67] Otherwise there is risk of gangrene or other evidence of acute or chronic ischemia. Sympathectomy before or during operation diminishes this complication.[90] Formerly, quadruple ligation of the artery and vein and simultaneous excision of the aneurysm were usually performed.[55, 64, 67] This obliterated a main artery. It appears probable that more satisfactory results, with less subsequent arterial insufficiency of an extremity, can be obtained by a transvenous arteriorrhaphy in which the arterial leak is repaired

while the vein is ligated.[71] If the blood volume is very high it may be desirable to perform a venesection at the time of operation to avoid flooding of the heart when the fistula is closed.

Treatment of congenital arteriovenous aneurysms is much more difficult because they are usually multiple and more extensive. The treatment of arteriovenous aneurysm of the lung has been mentioned. Congenital arteriovenous fistulas in the lower extremities may be treated conservatively by compression of the varices with pure rubber bandages.

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AORTIC STENOSIS

ETIOLOGY AND PATHOLOGY

Aortic stenosis has long been considered an uncommon valvular lesion. In recent years, however, a number of clinical, roentgenologic and pathologic reports have emphasized the relative frequency of this lesion and led to its recognition during life as well as post mortem. Clawson and his co-workers[9] reported 200 cases of calcified aortic valve out of 490 healed valvular deformities. More than 70 per cent of these 200 cases showed severe aortic stenosis. According to these figures, this is the commonest lesion of the aortic valve. Aortic stenosis of varying degree is often combined with mitral stenosis and aortic insufficiency, lesions whose clinical and pathologic features frequently overshadow or obscure those of aortic stenosis. Thus in Cabot's[5] series of 148 cases of predominant aortic insufficiency, 93 also had aortic stenosis, and in the series of McGinn and White,[34] of 159 cases of mitral stenosis 50 revealed a simultaneous aortic stenosis.

Noncalcific Aortic Stenosis. The *calcific* and *noncalcific* forms of aortic stenosis may be distinguished with respect to etiology and pathology. Noncalcific aortic stenosis is probably exclusively or almost exclusively due to rheumatic fever, and is usually associated with mitral stenosis and aortic insufficiency. It is encountered chiefly in patients below the age of fifty; males predominate only slightly.

The rheumatic inflammatory exudate produces thickening and deformity of the aortic valve.[27] It leads to agglutination of adjacent cusps by filling the commissures between them. With organization and scar formation, the valve cusps become thickened, firm and more or less fixed in position. The fixity of these rigid cusps and their adhesion to each other leads to the formation of a solid ring of fused leaflets which greatly narrow the circumference of the aortic orifice. The degree of narrowing is variable, but significant dynamic effects and clinical symptoms are produced only when the normal circumference, which averages 7.5 cm., is reduced to 5 cm. or less. Usually aortic insufficiency precedes stenosis and even when the latter is pronounced, some degree of insufficiency persists.

Calcific Aortic Stenosis. Calcific aortic stenosis is distinguished from the noncalcific form by its remarkable clinical symptoms, its predominant occurrence in males (two to five times as often as females) and the relatively advanced age of death.[7, 21, 36, 39] It is agreed that rheumatic fever causes almost

all of the cases of calcific aortic stenosis[8, 28] but some are undoubtedly of nonrheumatic etiology.[38, 21, 31] In 1904, Mönckeberg[35] distinguished a primary sclerocalcific form of aortic stenosis from that due to rheumatic fever on the basis of histologic differences (*Mönckeberg's ascending sclerosis, sclerosis annularis valvularum*). These differences have been confirmed by the pathologic studies of Geerling,[24] Giese[25] and more recently by Sohval and Gross.[38] The following are the essential pathologic distinctions: (1) In the rheumatic cases lipid and calcium secondarily infiltrate the preexisting rheumatic inflammatory lesions and scars. In the nonrheumatic cases sclerotic, lipoidal and calcific deposits are primary. (2) In the nonrheumatic valves, calcification begins and is most extensive in the sinus pocket and base of the valve, from where it progresses gradually to the free border. In rheumatic valves, the calcification begins and is most extensive in the distal third of the valve. (3) In the nonrheumatic valves, the calcific process affects primarily the fibrous layer of the valve cusp on the aortic surface of the leaflet. Calcification in rheumatic aortic valves occurs predominantly in the spongiosa and ventricularis layers on the ventricular aspect of the aortic cusp. (4) Rheumatic calcific aortic stenosis is frequently associated with rheumatic disease of the other valves, especially mitral stenosis; the nonrheumatic form is much more apt to be an isolated valvular lesion. In advanced cases the valve cusps, ring and commissures are entirely converted into a nodular stony mass and an etiologic diagnosis may be difficult or impossible.

The calcific sclerosis may involve structures adjacent to the aortic cusps and sinus pocket. The calcific process may extend by way of the intervalvular fibrosa, like the extension of a luetic aortitis, to implicate the anterior mitral cusp or the bundle of His in the interventricular septum.[46] The coronary ostia and arteries are often remarkably free of arteriosclerosis, but occasionally I have observed cases with myocardial infarction or fibrosis due to recent or old arteriosclerotic coronary occlusions. More frequently there are diffuse patchy areas of fibrosis or necrosis, without coronary narrowing or occlusion, and probably due to coronary insufficiency caused by the valvular lesion itself.[21, 20] Horan and Barnes[29] observed some degree of coronary atherosclerosis in all of their cases of calcareous aortic stenosis, but the amount of sclerosis was inversely proportional to the degree of valvular stenosis.

Aortic stenosis is rarely due to causes other than *rheumatic fever* or *degenerative calcific sclerosis*. *Active bacterial endocarditis* may produce a functional aortic stenosis by blocking the orifice with large vegetations. It is possible that healing of bacterial valvulitis may result in stenosis. Congenital aortic valvular or subaortic stenosis is discussed in Chapter 30. Syphilis per se does not produce an aortic stenosis. In 296 cases of aortic valvular disease studied by Campbell and Shackle,[6] 55 were due to syphilis, but all of these showed aortic insufficiency without stenosis. However, I have seen several cases in which a calcific aortic stenosis was apparently superimposed on or associated with a luetic aortic insufficiency, and similar cases have been reported.[22] In these cases one may occasionally see the characteristic syphilitic widening of one of the aortic commissures, while the others are obliterated by calcific masses which fuse adjacent leaflets.

The *heart in aortic stenosis* is usually considerably hypertrophied, and often weighs between 500 and 700 gm. The heart weight may be considerably less than 500 gm. when the stenosis is slight or moderate, and especially if death

occurs from some intercurrent cause before the development of cardiac failure. In some cases of asymptomatic aortic stenosis, accidentally discovered post mortem, I have seen normal heart weights.

In the relatively smaller hearts, the hypertrophy is entirely confined to the left ventricle. In the larger hearts, especially those weighing more than 500 gm., there is a considerable degree of visible dilatation as well as hypertrophy. When failure is present, the dilatation and hypertrophy involve the right as well as the left ventricle, and often also the atria.

PATHOLOGIC PHYSIOLOGY

Degree of Obstruction and Circulatory Disturbance. With slight aortic stenosis there may be no disturbances in circulatory dynamics, even when the lesion produces a loud systolic murmur. In experimental models and animals the aortic orifice must be reduced to approximately one quarter of its normal size to diminish significantly the cardiac output or alter pressure relationships.[1, 12] Such extreme lesions are common in human aortic stenosis, especially those associated with calcification. The effect of a severe experimental lesion is to increase the resistance to the outflow of blood from the left ventricle and cause incomplete emptying of that chamber.[41]

Compensations in Aortic Stenosis. The residual blood in the left ventricle due to its incomplete emptying is augmented by the normal inflow from the left atrium. The diastolic volume and pressure in the left ventricle rise. Compensation is effected in two ways:

(1) The increased diastolic volume and intraventricular pressure cause a more forceful systolic contraction with restoration of normal stroke output (Starling's Law of the Heart).

(2) There is a slight increase in the period of isometric contraction and a considerable prolongation of the ejection phase and of total systole. Thus the diminished output due to the obstruction is restored to normal in part by a more forceful systolic ejection and in part by prolongation of the period during which ejection occurs.

In humans these temporary mechanisms are eventually supported by the development of left ventricular hypertrophy. Because clinical aortic stenosis is a lesion which develops very gradually and over a period of many years, there is adequate opportunity for the production of considerable hypertrophy while the amount of dilatation remains relatively insignificant. When the stenosis is superimposed on a pronounced insufficiency or when cardiac failure supervenes, there may be extensive dilatation as well as hypertrophy.

CLINICAL FEATURES

Some distinction should be made between the clinical features of noncalcific and calcific aortic stenosis. The former is a rheumatic lesion, usually of only slight or moderate degree and combined with other valvular lesions which dominate the clinical picture. Calcific aortic stenosis may or may not be due to rheumatic fever, is frequently the sole or predominant lesion and is generally of extreme severity. The interesting and characteristic clinical picture which we have come to associate with aortic stenosis, and which will be described here, applies essentially to the calcific form of the disease.

Compensated Aortic Stenosis. Compensated aortic stenosis is often asympto-

matic, being discovered as an accidental postmortem finding. Only 6 of the 42 patients in the series studied by Margolis and his co-workers[32] complained of symptoms referable to the circulation. However, in many cases, especially late in the course of the disease and when the valvular obstruction is extreme, a number of characteristic symptoms may develop even when compensation appears adequate. These symptoms, including dizziness, syncope or cardiac pain, may occur prior or subsequent to the development of cardiac failure.

Angina Pectoris in Aortic Stenosis. Cardiac pain has been noted in 10 to 20 per cent of proven cases of aortic stenosis. In my experience the incidence is much higher if the diagnosis of aortic stenosis is made clinically and the patient is queried specifically with regard to cardiac pain. Angina pectoris occurs more frequently in aortic stenosis than in other valvular lesions. Its occurrence in luetic aortic insufficiency is generally due not to the valvular lesion as such but to the syphilitic narrowing of the coronary ostia (p. 821).

The cardiac pain is usually a typical angina pectoris of effort, located over the sternum or precordium and radiating to the left arm. Boas[4] reported several cases in which the cardiac pain resembled the excruciating, persistent variety seen in coronary thrombosis. I have personally observed 3 cases in which death occurred with the clinical and electrocardiographic picture of acute coronary occlusion.

The pathogenesis of the cardiac pain is still uncertain, a number of possible explanations having been offered: (1) Because of the frequent presence of a diastolic murmur in calcific aortic stenosis, the cardiac pain has been ascribed to an associated aortic insufficiency. This explanation is unlikely because despite the diastolic murmur there is rarely a dynamically significant insufficiency. Nor is angina pectoris frequent in uncomplicated aortic insufficiency. Furthermore, I have observed angina pectoris in cases of aortic stenosis in which there was no diastolic murmur nor any other clinical evidence of a possible aortic insufficiency. (2) Boas[4] believed that the pain was caused by myocardial ischemia due to the obstruction at the aortic orifice. But there is no clear explanation as to the mechanism of this ischemia, since a normal aortic pressure is often maintained despite the stenosis. (3) Contratto and Levine[10] ascribed the angina pectoris to a relative myocardial ischemia caused by the increased velocity of blood flowing past the coronary orifices. This was said to result in a tendency to withdraw blood from the coronary vessels by suction. This is hypothetical.

Personal studies support the concept of myocardial anoxia as the basis of cardiac pain in aortic stenosis. The pathogenesis of this anoxia varies in different cases: (1) Despite the fact that the coronary arteries in aortic stenosis are usually surprisingly smooth, not infrequently there is severe *coronary sclerosis with narrowing of the lumina.* Thus angina pectoris in some cases of aortic stenosis is due to the same cause as in cases without valvular disease, namely *coronary narrowing with consequent myocardial anoxia.* This may be exacerbated by occasional narrowing of the coronary ostia by calcific deposits in the sinus pockets. (2) Acute *coronary thrombosis,* which may occur as a result of coronary artery disease, accounts for most of the cases in which there is an attack of prolonged, excruciating cardiac pain. (3) Myocardial ischemia may result from *functional coronary insufficiency* with or without associated coronary artery narrowing.[20] This merits special discussion.

Coronary Insufficiency in Aortic Stenosis. The existence of coronary insufficiency in aortic stenosis is supported by clinical, pathologic, physiologic and electrocardiographic observations. The occurrence of angina pectoris in cases with relatively normal coronary vessels has been noted; it suggests that there is a physiologic inadequacy in coronary flow despite the absence of mechanical obstruction. We have found pathologic support for this concept in a number of cases of aortic stenosis, carefully studied at autopsy. In several of these cases in which the most detailed search failed to reveal an acute coronary occlusion, I have encountered acute myocardial damage varying in extent from focal areas of necrosis to extensive myomalacia.[21, 20] In the more severe cases, the clinical picture and electrocardiographic changes were those of acute myocardial infarction. These are examples of intense functional coronary insufficiency. But it is reasonable to assume that similar, less intensive myocardial ischemia may account for the cases of angina pectoris without anatomic change either in the myocardium or the coronary vessels.

Physiologic support for coronary insufficiency in aortic stenosis is found in the experiments of Green.[26] He demonstrated that there was a significant reduction in the minute flow through the coronary arteries and that this flow could not easily be increased when the myocardial demand for blood was increased. Even with extreme aortic stenosis, an essentially normal aortic pressure is often maintained by an increased left ventricular contraction associated with a tremendous elevation of intraventricular pressure. But the latter diminishes the systolic flow (and minute flow) of blood through the coronary arteries by producing an increased peripheral coronary resistance during systole. Thus there may be an inadequate coronary flow even at rest. This deficiency is greatly increased by exertion, since the left ventricle finds it difficult or impossible to augment further the force of its contraction and the aortic pressure.

Conduction Disturbances in Aortic Stenosis. Complete heart block, bundle branch block, intraventricular conduction defects and delayed auriculoventricular conduction occur with sufficient frequency in calcific aortic stenosis to be considered features of the disease.

The cause of the conduction defects, especially of complete heart block, has been found in organic disease of the bundle of His, due to an extension of the calcific process from the aortic valve to the fibrous septum.[42] While I, as well as others, have observed such calcific obstruction of the bundle, I have also seen various grades of heart block in cases in which such organic changes could not be demonstrated. There are additional reasons for believing that the conduction disturbances are not invariably, nor even usually, due to organic interference with conduction by calcium deposits. The type and grade of conduction disturbance in a given case vary from time to time. Thus in one case of calcific aortic stenosis which I observed, the electrocardiogram first revealed only a left axis deviation and a negative T wave in lead I. A week later the P-R interval was prolonged to 0.28 second; shortly afterward there was a transient, complete heart block, and eventually an intraventricular conduction disturbance. In one case in Boas'[4] series, heart block was likewise transient and occurred only on exertion. Angina pectoris developed simultaneously. It is difficult to correlate these observations with a fixed, organic lesion (lime) in the bundle or its main branches. On the other hand, they are compatible with the belief that the disturbances in conduction, like the cardiac pain, are due to

myocardial ischemia caused by functional coronary insufficiency. Occasionally, also, coronary arteriosclerosis plays a contributory role. The calcification in the septum may be an underlying or predisposing factor.

Dizziness and Syncope in Aortic Stenosis. On careful questioning, one can often elicit a history of dizziness or faintness, especially with exertion or change of position. Not infrequently there are more severe attacks associated with syncope, which may last for fifteen to thirty minutes. McGinn and White[34] noted this symptom in 31 out of 98 clinical cases. Gallavardin[23] and his students have stressed the frequency of syncope of effort in aortic stenosis. Occasionally there are petit mal seizures or hemiparesis.[30]

Several explanations have been offered for the occurrence of dizziness and syncope in this disease: (1) Marvin and Sullivan[33] suggested that syncope is due to a hyperactive carotid sinus reflex. Contratto and Levine[10] were able to confirm the presence of a hypersensitive carotid sinus in some cases of aortic stenosis with syncope but not in others. (2) Gallavardin[23] believed the syncope to be due to a sudden, transient cerebral anemia caused by an insufficient aortic output. This theory was based on an electrocardiographic observation, made during syncope of effort, that the heart did not stop contracting while the pulse beat disappeared. But no explanation is afforded as to why the aortic output suddenly became inadequate. (3) A third explanation, which we have suggested,[21] attempts to clarify not only the cause of the syncope but also its occurrence during effort and in individuals who suffer from angina pectoris. Both syncope and angina pectoris occur in those individuals in whom the degree of aortic narrowing and consequently the compensatory left ventricular hypertrophy are extreme. With usual activity, a normal aortic and consequently a normal cerebral arterial circulation is maintained in these individuals by a tremendously elevated left intraventricular pressure. But so little reserve is left for further elevation of this pressure that it cannot be augmented adequately or with sufficient speed when exertion requires an increased cerebral vascular flow. Thus with effort, dizziness and syncope result from the cerebral anemia due to cerebral arterial insufficiency. As we have seen above (p. 608), similar events in these individuals lead to coronary insufficiency and angina pectoris, especially with effort. But syncopal attacks may occur in such patients without anginal symptoms.

The above explanation does not preclude the occurrence of syncope as a result of a hyperactive carotid sinus reflex in some cases. In still others, syncope may be one of the manifestations of an Adams-Stokes syndrome due to the complete heart block occasionally present in aortic stenosis.

Sudden Death in Aortic Stenosis. The frequency of sudden death in calcific aortic stenosis has been repeatedly noted, but its pathogenesis remains obscure. Of 76 cases followed by Willius,[44] 8 had died suddenly. Reports of sudden death are also found in 5 to 15 per cent of the cases of McGinn and White,[34] Contratto and Levine[10] and of Margolis and his co-workers.[32] Marvin and Sullivan[33] gave a detailed account of 9 cases of sudden death in calcific aortic stenosis. Sudden death often occurs in individuals who have previously suffered from dizziness, syncope or angina pectoris, and its occurrence may be an extreme expression of the same factors which produce the latter symptoms. Sudden death may occur in patients with aortic stenosis with or without cardiac failure.

There are probably multiple causes of sudden death in aortic stenosis:

(1) The commonest cause of sudden death in general is coronary artery occlusion. As we have mentioned, although the coronary arteries are usually fairly normal in aortic stenosis, occasionally there is a typical acute coronary artery thrombus with myocardial infarction.

(2) In other cases of aortic stenosis with open coronary vessels, myocardial infarction is occasionally seen as a result of extreme coronary insufficiency. This may also account for sudden death. In still other cases, similar severe myocardial ischemia may cause death so rapidly that there is insufficient time for the development of an infarct.

(3) Severe myocardial ischemia may produce a high degree of heart block which may be associated with cerebral anemia, cardiac standstill or ventricular fibrillation. These are all theoretical causes of sudden death.

(4) Cerebral anemia, which in some patients produces dizziness or syncope, may, if extreme, result in sudden death.

(5) A hypersensitive carotid sinus may produce cardiac standstill and sudden death. In some patients this outcome may be the result of a combination of factors. Thus reflexes from a hypersensitive carotid sinus may more readily cause sudden death if there is already some degree of myocardial ischemia and conduction disturbance.

(6) Two cases have been reported in which sudden death may have resulted from the formation of an occluding thrombus over the stenotic valvular orifice.[33] In one case, it was suggested, death was due to occlusion of the aortic orifice when one cusp became locked under a shelf formed by the other two.[13]

Left Heart Failure in Aortic Stenosis. Symptoms of left ventricular failure are often the first subjective manifestations of the disease. *Dyspnea on exertion* is the earliest and most frequent symptom. This may be present for a year or two, rarely longer, before other symptoms develop. The dyspnea often becomes much more intense a few weeks or months before the end. Attacks of *nocturnal paroxysmal dyspnea* (cardiac asthma) are not infrequent. While they usually develop later in the course of the disease than exertional dyspnea, I have seen two patients in whom such nocturnal attacks were present for months before there was any respiratory disturbance during the day. In both of these patients, there was an associated "free" aortic insufficiency. *Insomnia and nightmares,* with or without associated cardiac asthma, occasionally occur when there is early heart failure. Cough and expectoration are not infrequent, and rarely there is hemoptysis. *Orthopnea* is a late and frequent manifestation, occurring when the exertional dyspnea is quite severe.

Right Heart Failure in Aortic Stenosis. As in aortic insufficiency, definite failure of the left ventricle soon leads to pulmonary congestion, elevated pulmonary arterial pressure and strain on the right ventricle. Failure of that chamber follows shortly. In the patients I have observed, the symptoms of left heart failure did not subside when evidences of systemic venous engorgement developed as a result of right heart failure. Peripheral edema appears when dyspnea and orthopnea are severe. The course of the disease thereafter is rapidly progressive. The liver becomes huge, reaching to the level of the umbilicus. The cervical veins are distended and may pulsate. The venous pressure is elevated. Cyanosis appears toward the very end of the disease. Effusions in the serous cavities are not uncommon, particularly hydrothorax. Frequently, weakness, loss of weight and emaciation are prominent near the termination.

Objective Findings in Aortic Stenosis

The Heart. *Inspection* and *percussion* are usually of little assistance, especially in elderly persons in whom a rigid, barrel-shaped chest obscures the pulsations of the heart. In younger persons, one may occasionally note a slow, lifting pulsation of the hypertrophied heart.

Palpation is important as it may supply a leading clue to the diagnosis. There is frequently a *systolic thrill* at the base of the heart, to the right of the sternum or along the right cervical vessels. Its frequency in verified cases has undoubtedly been understated because this sign is not always specifically sought when the diagnosis of aortic stenosis is unsuspected. Occasionally it can only be elicited if the patient sits or stands and bends forward.

Auscultation reveals a long-drawn, loud and usually rough or rasping systolic murmur over the aortic area and the cervical vessels. The murmur may radiate not only to the neck, but downward along the sternum toward the apex and occasionally to the back. Occasionally the systolic murmur is most prominent at the apex of the heart. An apical systolic murmur may represent a radiation from the aortic area or a complicating relative mitral insufficiency when left ventricular failure occurs.

The *second sound* over the aortic area is characteristically faint or absent. Not infrequently, however, it is unaltered. Its absence indicates extreme fixation of the aortic cusp.

A *diastolic murmur* over the base of the heart is heard in almost half the cases of "pure" monovalvular aortic stenosis. It is rarely accompanied by the peripheral circulatory signs of aortic insufficiency.

In addition to the above auscultatory signs of aortic stenosis, there are often those of an associated mitral stenosis. McGinn and White[34] found this lesion present in over 40 per cent of their cases of aortic stenosis. The physical signs of mitral stenosis in these cases may easily overshadow and obscure those of aortic stenosis.

Pulse and Blood Pressure. The pulse in severe aortic stenosis is often characteristic. It is of small amplitude, rises slowly and falls away slowly (pulsus parvus et tardus). Its slow, prolonged elevation (systolic ejection being prolonged in aortic stenosis) gives it the form of a plateau. There is an actual delay in the arrival of the pulse at the radial artery as compared with that of the normal pulse. In aortic stenosis, the interval between the apex beat and the radial pulse is 0.2 second instead of the normal interval of 0.07 to 0.1 second.

Pulse tracings from the radial artery often show a slight anacrotic notch on the ascending limb. Hence the pulse of aortic stenosis has sometimes been described as an *anacrotic pulse*. The greater the stenosis the lower is the position of this notch.[43] When, rarely, the notch is quite sharp, a double peak is formed and the wave is described as pulsus bisferiens. Vibrations at the height of the carotid pulse have been termed carotid shudder.[17] Feil and Katz[18] have shown that the anacrotic notch in aortic stenosis is not present in the central arteries, e. g., in the subclavian. Its appearance in the radial artery is merely the peripheral wave manifestation of the sudden change in pressure (recoil) in the aorta when the narrowed aortic orifice offers marked resistance to flow after the first rapid ventricular ejection of blood.[14]

The *blood pressure* in uncomplicated cases is normal. Sometimes, however, the systolic pressure is slightly diminished, and the diastolic is normal or

slightly elevated, with a resultant small pulse pressure. There is often a prominent auscultatory gap. In various series, both the average systolic pressure and the average pulse pressure are elevated because of an associated free aortic insufficiency or essential hypertension in many of the cases. Contratto and Levine[10] found 17 cases of hypertension in their series of 180. The average blood pressure was 145/84, the range being between 260/156 and 80/10. In one case of calcific aortic stenosis combined with syphilitic aortic insufficiency, I observed a blood pressure of 300/40.

Roentgenologic Examination of the Heart in Aortic Stenosis. In uncomplicated, well compensated aortic stenosis, the cardiac silhouette may appear normal even when there is slight hypertrophy. There is usually hypertrophy of the outflow tract of the left ventricle with relatively little dilatation. In anteroposterior views, this is indicated by a blunt rounding of the lower left cardiac contour (Fig. 6*A*, p. 26). By fluoroscopy or roentgenkymography, one may observe a slow ventricular thrust or a gradual prolonged systolic contraction. When left heart failure develops, the heart may become "mitralized" as in aortic insufficiency (p. 595). When right heart failure also develops, the cardiac shadow shows universal enlargement to the left and right.

The aortic shadow in "pure" aortic stenosis, in contrast with that of aortic insufficiency, is either normal or diminished in size and pulsation.

Roentgenologic examination of the heart has assumed special importance in the diagnosis of the calcific type of aortic stenosis. Fleischner[19] first diagnosed calcification of the annulus fibrosus during life, and subsequently Sosman and Wosika,[40] Willius and Camp,[45] Bishop and Roesler[3] and others[16] have reported series of verified cases in which antemortem diagnoses of calcified mitral and aortic valves were made by roentgenologic examination. The calcification can be demonstrated fluoroscopically and on films. In fluoroscopy, it is important to be extremely well accommodated, and to use a beam of high penetration coming through a very small aperture in the screen. The calcified deposits should be localized by rotating the patient so as to determine the best views.*

Fluoroscopically, the calcified valves appear as dense nodular pulsating shadows which are described as dancing in a jerky fashion. Their excursion is greater than that of the cardiac borders (1 to 2 cm.) and is best observed in the oblique views and by roentgenkymography.[11] They are not apparently affected by deep respiration. The calcified valves are seen slightly to the left of the midline (in a slight right oblique position which removes them from the dense spine shadow) and in the lowest third of the cardiac shadow near the junction with the middle third. The mitral valve is in the posterior third of the cardiac shadow, and the aortic valve slightly anterior and caudad to it. The motion of these shadows is rotatory or elliptical, their direction being downward and toward the apex in systole, and upward and toward the midline in diastole. Both valves may be calcified. Calcification of the annulus fibrosis[19] may be distinguished from calcification of the cusps by a tendency to ring-like forms and less pulsation (Fig. 58). The discovery of calcification of the aortic valve on roentgenologic examination does not necessarily indicate aortic stenosis. But such discovery is a strong diagnostic confirmation when aortic stenosis is suspected clinically. Calcification of the valves may be distinguished from cal-

* Improved results have been reported with a new technic using cardiac tomography. (Davies, C. E., and Steiner, R. E.: Brit. Heart J., *11*:126, 1949.)

cified pericardium, calcified tumors, thrombi or aneurysms of the heart by the characteristic shape, position and pulsation of the calcified valves. They can be distinguished from calcified lymph nodes and other extracardiac calcifications by the fact that calcified valvular shadows cannot be projected outside the cardiac outlines on rotating the patient.

The Electrocardiogram in Aortic Stenosis. The electrocardiogram may be normal or show only a left axis deviation if there is no associated mitral stenosis Not infrequently, however, there are (1) permanent or transient severe conduction disturbances and (2) abnormalities of the T waves and RS-T transitions similar to those seen in coronary artery disease.

The conduction disturbances in order of frequency appear to be left bundle branch block, intraventricular conduction defects, partial and complete heart block.[46] I have seen cases in which the electrocardiograms showed first one, then another and even a third of these disturbances at different times.

The abnormalities of the T waves, RS-T transitions and of the QRS complexes closely simulate those of myocardial damage due to coronary artery disease[2] and, in my opinion, the changes in both conditions are due to functional coronary insufficiency and myocardial ischemia. The T waves may be diphasic or inverted in one or more leads. They may have the characteristic cove plane or seagull appearance seen in coronary occlusion. The RS-T transitions are concordantly depressed. The QRS complexes are not infrequently of low voltage, notched, slurred and prolonged.

Auricular fibrillation is uncommon in "pure," monovalvular aortic stenosis,[15] its relative frequency in some reported series being merely a feature of an associated mitral stenosis.

Complications of Aortic Stenosis

Heart failure occurs most often and is the commonest cause of death. Sudden death is not infrequent. Subacute bacterial endocarditis is uncommon except in cases with predominant aortic insufficiency. Myocardial infarction with or without coronary thrombosis is occasionally observed. The Adams-Stokes syndrome may be a fatal complication. Bronchopneumonia, pulmonary infarction and acute pulmonary edema are occasional complications which may result fatally.

DIAGNOSIS

The diagnosis is simple if the classical, cardinal criteria are satisfied, namely: (1) a loud, rough, aortic systolic murmur, (2) an aortic systolic thrill, (3) absent or faint second aortic sound and (4) a characteristic small, delayed pulse. The most common oversight is failure to palpate the chest wall for a thrill. When an associated mitral stenosis dominates the clinical features, an aortic stenosis may be easily overlooked unless two or more of these signs are present. Usually the murmur and thrill suffice to justify the diagnosis. The finding of calcification of the aortic valves on roentgenologic examination and the characteristic pulse tracings are confirmatory. The presence of an aortic murmur for many years in a middle-aged or elderly male should suggest the possibility of calcific aortic stenosis, especially if such a murmur is associated with a history of angina pectoris, dizziness, or syncope. In the absence of syphilis or a positive Wassermann reaction, and in the absence of the peripheral signs

of aortic insufficiency, a combined systolic and diastolic murmur over the aortic area should suggest calcific aortic stenosis. In cases of mild aortic stenosis a diagnosis of calcific aortic stenosis may have to be ventured merely on the basis of a rough aortic systolic murmur and the fluoroscopic demonstration of a calcified aortic valve.

Differential Diagnosis. Aortic stenosis is commonly mistaken for *arteriosclerotic heart disease,* i. e., *coronary artery disease.* Attacks of dizziness and syncope on effort, when present, favor the diagnosis of aortic stenosis rather than coronary artery disease. If the syncope is due to heart block, the etiology may be either coronary arteriosclerosis or aortic stenosis. Search should be made for the distinctive murmur, the aortic systolic thrill and the characteristic pulse and aortic valvular calcification. Acute myocardial infarction or pulmonary embolism is mistakenly diagnosed if the patient develops acute circulatory failure (shock) or dies suddenly.

Mitral insufficiency may be diagnosed because of the systolic murmur, which may be quite loud over the apex of the heart. Uncomplicated mitral insufficiency is rare after fifty. In young individuals, the history and cardiac configuration should distinguish the two conditions. *Aortic insufficiency* is more apt to be diagnosed than aortic stenosis when, as often happens, there is an associated aortic diastolic murmur. In the absence of syphilis or an associated mitral lesion, the probability of calcific aortic stenosis should be investigated.

Congenital cardiac lesions, such as patent interventricular septum, pulmonic stenosis, or patent ductus arteriosus, are sometimes diagnosed. The youth of the patient, the history of the lesion very early in life, the cardiac contour and right axis deviation distinguish these lesions. (But see aortic stenosis p. 676.)

An aortic murmur and thrill may also result from thoracic tumors, or aneurysms with compression of the aorta or subclavian vessels. These lesions are usually easily distinguished by roentgen ray examination of the chest.

PROGNOSIS AND TREATMENT

Individuals with pure aortic stenosis, especially the calcific form of the disease, have a good prognosis and are usually long-lived. The outlook remains favorable only so long as compensation is maintained. Clawson, Bell and Hartzell[8] found the average age at death of 29 cases with predominant aortic stenosis to be 55.8 years as compared with an average age of 41.7 years for mitral stenosis. Clawson, Noble and Lufkin[9] found that the majority of their 200 cases survived until the seventh decade or later.

The occurrence of angina pectoris or syncopal attacks is unfavorable. Once heart failure develops, the prognosis is extremely poor and the course of the disease is rapidly progressive. Contratto and Levine[10] noted the occurrence of death in aortic stenosis on an average of 23 months after the onset of dyspnea, 9.3 months after the onset of peripheral edema, 9 months after the onset of syncope, 6 months after the appearance of râles in the lungs, and 4 months after the development of the first attack of pulmonary edema.

The *treatment* is symptomatic. Restriction of activity or modification of forms of activity may be indicated when there is angina pectoris or syncope of effort. Vasodilators such as nitroglycerin may be required for cardiac pain. The treatment of syncope or heart failure is discussed elsewhere. Studies of the possibility of performing an aortic valvulotomy are still in the experimental stage.[37]

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29

TRICUSPID AND PULMONIC VALVULAR DISEASE

TRICUSPID VALVULAR DISEASE

Etiology

Tricuspid insufficiency is usually a functional disturbance but may be due to organic disease of the valve.

Organic tricuspid insufficiency is almost always caused by rheumatic fever, but it may occasionally result from trauma, which tears a cusp or ruptures its chordae or papillary muscle. Rarely bacterial endocarditis causes or increases a tricuspid insufficiency. Congenital tricuspid insufficiency is rare, and may be due to incomplete differentiation of the cusps or to a downward displacement of the right ventricle (Ebstein type)[11, 6] (p. 677).

Frequent involvement of the tricuspid valve in rheumatic heart disease was noted by Sansom.[30] There is almost always concomitant rheumatic mitral disease, and often also aortic valvular involvement. Gross and Friedberg[16] found microscopic evidence of rheumatic inflammation in the tricuspid valve almost as often as in the mitral, but significant insufficiency or stenosis is uncommon.

Functional tricuspid insufficiency occurs in a great variety of conditions associated with failure and dilatation of the right ventricle. When the right ventricle fails, the tricuspid valve becomes insufficient for two reasons: (1) Weakness of the right ventricular contraction removes the important muscular factor normally necessary to close the tricuspid orifice completely.[20] For even normally there is a slight, physiologic tricuspid insufficiency because the tricuspid leaflets are not quite large enough to close the tricuspid orifice. Effective muscular contraction, which narrows the tricuspid ring, is important for complete closure of the tricuspid valve. (2) Failure of the right ventricle is associated with enlargement of its chamber and consequent retraction of the papillary muscles and their attached chordae tendineae from the tricuspid valve. Thus the tricuspid leaflets are held taut within the ventricular chamber and are unable to move sufficiently to close the orifice. At the same time dilatation of the right ventricle stretches the tricuspid ring and enlarges the orifice.

Tricuspid stenosis is less common than tricuspid insufficiency but not so rare as was formerly believed.[10, 48, 15, 2] As a rule, insufficiency is associated with tricuspid stenosis.[15] Tricuspid stenosis is almost always associated with

a more severe mitral stenosis, the latter being present in all 30 cases of tricuspid stenosis reported by Dressler and Fischer,[10] and in 181 of the 195 cases reported by Futcher.[14] Aortic insufficiency or stenosis is also associated in one half to two thirds of the cases. Occasionally tricuspid stenosis is said to occur as an isolated lesion, e. g., in 14 of the 187 cases collected by Herrick.[18] Tricuspid stenosis may be associated with disease of the other three valves.[17]

Tricuspid stenosis may be congenital or acquired. The congenital lesion is very rare and occurs as a ventricular malformation with atresia of the orifice, or is due to adhesion of the free borders of the valve (p. 677).

Acquired tricuspid stenosis is almost invariably due to rheumatic fever, but occasionally a functional tricuspid stenosis results from bacterial vegetations, thrombi or tumors projecting into the tricuspid orifice. The obstructing vegetations, which are polypoid and massive, occur in bacterial endocarditis. Obstructing atrial thrombi occur rarely in cases of heart failure with auricular fibrillation,[47] or in cases of myocardial infarction with a mural thrombus occluding the tricuspid valve from below. The tumors are usually primary myxoma or sarcoma or secondary metastases of hypernephroma, sarcoma of the testis, carcinoma of the thyroid or other neoplasms.

Tricuspid stenosis has been found by Smith and Levine[34] in 10 per cent of 340 and by Cooke and White[8] in 15 per cent of 217 autopsied cases of rheumatic heart disease. These and other observers have noted additional cases of rheumatic involvement of the tricuspid valve without significant deformity. In still other cases of rheumatic tricuspid valvular disease, no differentiation is made between stenosis and insufficiency. Among 147 autopsied cases of rheumatic heart disease reported by Aceves and Carral[2] 50 per cent had some tricuspid involvement and 33 per cent (49 cases) had a valvular deformity classified as tricuspid insufficiency. Of the latter 49 cases, 11 disclosed predominant stenosis and another 11 equally marked stenosis and insufficiency.

Age and Sex. These are the same as in patients with other rheumatic valvular lesions. The usual age is between twenty-five and forty for the organic rheumatic cases of tricuspid valvular disease, but occasional cases are encountered in persons beyond the age of fifty. There is a distinct predominance of females, especially among those with pronounced tricuspid stenosis.

Pathology

The pathologic findings in the valves are described in the chapters on the causative disease (i. e., rheumatic fever, congenital heart disease, etc.). In the rheumatic cases the cusps undergo inflammatory swelling and thickening which interfere with their proper coaptation. Closure of the tricuspid orifice is further impaired by shortening and retraction of the cusps and their chordae. Tricuspid insufficiency is enhanced when dilatation of the right ventricle is associated with concomitant dilatation of the tricuspid ring. Tricuspid stenosis is the predominating disturbance when rheumatic inflammation and scarring causes adhesion of the cusps to each other. This leads to a single, fused, cylindrical or conical curtain or more rarely to a buttonhole type of stenosis. Some degree of tricuspid insufficiency is associated. The associated mitral stenosis is almost always more pronounced than the tricuspid stenosis.

Bacterial endocarditis may enhance a rheumatic tricuspid stenosis by forming a large obstructing vegetation or increase an insufficiency by destruction of a cusp or chordae. However, the tricuspid valve is uncommonly involved in

bacterial endocarditis. Following intravenous injection of heroin in addicts there may occur an isolated staphylococcus or other bacterial endocarditis of the tricuspid valve.

The Heart. The size of the heart and of the individual chambers is determined in part by associated lesions. The right atrium is dilated and hypertrophied with both tricuspid insufficiency and stenosis. In tricuspid stenosis the right atrium may be so enormous that it appears as a supplemental heart, and in Taussig's[39] case it was the only hypertrophied chamber. Sometimes the dilated right atrium appears as a huge fibrous sac, in which the muscle has undergone atrophy.

The right ventricle is dilated and hypertrophied both in organic and functional tricuspid insufficiency. In the presence of pronounced tricuspid stenosis the right ventricle may be normal in size or only slightly hypertrophied. The associated mitral stenosis often causes right ventricular hypertrophy of some degree, but this is less pronounced when the tricuspid stenosis is marked than when it is slight.

The left atrium is usually dilated and hypertrophied in organic tricuspid stenosis or insufficiency because of the concomitant mitral stenosis. In cases of functional tricuspid insufficiency the left atrium may be dilated and hypertrophied if left-sided heart failure preceded failure of the right heart, but not if the latter is due to cor pulmonale.

The size of the left ventricle is determined by the presence, order of development and predominance of mitral stenosis or of an aortic valvular lesion.

The *venae cavae,* especially the inferior, are prominently dilated and may form a continuous sac with the dilated right atrium. As a result of venous stasis, the internal viscera, particularly the liver, spleen and kidneys, show severe chronic passive congestion. Cardiac cirrhosis of the liver is more frequent than in other forms of valvular disease and heart failure.

Pathologic Physiology

Both with tricuspid stenosis and insufficiency there is an increased diastolic volume of blood in the right atrium. In the former it is due to incomplete emptying through the narrowed valvular orifice, in the latter to regurgitation of blood into the atrium during right ventricular contraction. The increased stretch results in a more forceful atrial contraction with at least a temporary restoration of normal output. During this process of compensation the right atrium becomes dilated and eventually hypertrophied.

Because of the limited compensatory capacity of the thin right atrial wall, systemic venous distention occurs early. This serves to diminish the outflow from the right side of the heart and reduces or prevents pulmonary engorgement. When tricuspid stenosis is the predominant lesion, its effect is somewhat similar to that of constrictive pericarditis in that it obstructs the inflow of blood into the right ventricle.

The dynamics of tricuspid lesions may be modified and are often overshadowed by those of associated mitral or aortic valvular disease. In the instances of functional tricuspid insufficiency the prevailing circulatory dynamics are determined by the conditions which produce ventricular dilatation and failure.

Intracardiac catheterization has disclosed characteristic pressure tracings in cases of tricuspid insufficiency. In cases of right-sided heart failure with competent tricuspid valve there is a pronounced drop in atrial pressure early in

ventricular systole due to descent of the tricuspid valve. But when the tricuspid valve is insufficient, blood spurts back into the atrium during systole and the atrial pressure is unchanged or rises instead of falling.[29]

Clinical Features

The clinical picture of tricuspid valvular disease resembles that of advanced right-sided heart failure with systemic venous engorgement. In cases of organic tricuspid disease there is usually a preceding period of known mitral stenosis or of mitral and aortic valvular disease, with or without left-sided heart failure. When organic tricuspid disease is added, the clinical picture may be indistinguishable from that of mitral and aortic valvular disease with heart failure, or it may be dominated by the effects of the tricuspid lesion.

The clinical features of pure tricuspid insufficiency may be gleaned from rare cases of traumatic origin. Todd[43] reported the case of a man of twenty-one who, following a stab wound in the right chest, suffered a rupture of the chordae tendineae of the anterior cusp of the tricuspid valve. Two and a half years later he was in advanced right heart failure with hepatic enlargement, widespread anasarca and ascites.

In cases of functional tricuspid insufficiency the clinical picture is characterized by the combination of left and right-sided heart failure or of primary pulmonary disease with secondary right heart failure.

Dyspnea on exertion is the commonest subjective symptom, probably due to pulmonary congestion caused by a concomitant mitral stenosis or other lesion producing left-sided failure.[38] However, the remarkable feature of tricuspid disease is the relative freedom from orthopnea and paroxysmal dyspnea. Sometimes the development of tricuspid stenosis or insufficiency is documented by partial or complete relief of preceding dyspnea and orthopnea due to left-sided heart failure. This relief in pulmonary congestion is regarded as the consequence of diminished right ventricular output into the lungs, because of the tricuspid lesion.

Persistence of dyspnea in the presence of tricuspid valvular disease may be due to hydrothorax, or the pressure of abdominal ascites. When functional tricuspid insufficiency follows cor pulmonale and right heart failure, dyspnea persists because of the primary pulmonary disease.

Other subjective symptoms include anorexia, nausea, eructations, vomiting and abdominal pain due to chronic passive congestion of the gastrointestinal tract, to enlargement of the liver or to ascites. Rarely hematemesis or melena occurs from secondary ulceration of the congested, inflamed mucosa of the gastrointestinal tract.

Objective Signs. *Cyanosis* is a frequent finding. It is due essentially to long-standing pulmonary congestion secondary to mitral stenosis or to preceding pulmonary disease. Pulmonary infarction may be a contributing or primary causative factor. Pronounced slowing of the blood stream with peripheral stasis may also contribute to cyanosis by increasing the tissue extraction of oxygen from the capillaries.[4]

Cyanosis is usually more pronounced and dyspnea less pronounced in cases of tricuspid and mitral stenosis than in mitral stenosis alone. This may denote that the relief of pulmonary engorgement afforded by the tricuspid lesion diminishes the rigidity of the lung and thereby alleviates dyspnea. On the other hand, in the presence of tricuspid disease, the associated mitral stenosis is

almost always very severe and the fibrosis and thickening of the pulmonary alveolar septa are pronounced. The latter changes impair aeration of the blood. Thus arterial anoxemia and cyanosis result from poor aeration of the pulmonary capillary blood, even though pulmonary ventilation improves as the vascular congestion diminishes. Secondary *polycythemia* may develop as a compensation to the anoxemia.

Icterus or a subicteric tint is often combined with the cyanosis in the cases of organic tricuspid disease. The resulting yellowish blue or olive coloration often suggests the diagnosis.[10, 46] The jaundice is probably due to hepatic dysfunction caused by longstanding congestion and fibrosis of the liver. Frequent *pulmonary infarcts* seen in organic tricuspid disease have also been held responsible as a contributing causative factor (p. 125).

Hepatic enlargement is a constant finding. The liver may be huge. There is usually a systolic liver pulsation in cases of tricuspid insufficiency or a presystolic pulsation in cases of tricuspid stenosis (infra).

Venous engorgement, especially of the cervical veins, is a striking feature of tricuspid disease. There is a pronounced systolic pulsation with tricuspid insufficiency and a characteristic double pulsation with tricuspid stenosis, provided the rhythm is regular. Similar venous distention and pulsation may be visible in the more peripheral veins such as the basilic veins and those in the dorsum of the hands.[40, 19] The *venous pressure* is greatly elevated and increases with pressure over the right upper quadrant of the abdomen (hepatojugular reflux). The *circulation time* is increased.

Ascites is a predominant manifestation. Its early development, its relatively long duration, its recurrence despite repeated abdominal tappings are characteristic features.[42, 18] In cases of tricuspid stenosis and to a lesser extent in cases of tricuspid insufficiency peripheral edema may be absent or relatively slight in contrast with the usual findings in right-sided heart failure.[3] In cases of functional tricuspid insufficiency edema is usually present. Effusions in the pleural cavities are common in all types of tricuspid valvular disease.

The explanation for the early and disproportionate ascites in tricuspid stenosis is unknown. Extreme, rapid and prolonged congestion of the liver may account for the predominant ascites reminiscent of hepatic cirrhosis. Eventually edema of variable degree develops in most cases of tricuspid disease. *Hypoproteinemia* due to hepatic dysfunction is an important contributory factor. The edema may also involve the face, since patients with tricuspid stenosis do not usually suffer from orthopnea and lie flat in bed.

Systolic or Positive Venous Pulse in Tricuspid Insufficiency. Normally three waves are observed in the jugular venous pulse. These pulsations are determined by pressure changes in the right atrium which are reflected in the jugular vein. The first or "a" wave occurs shortly before the apical impulse and is due to right atrial contraction. The second or "c" wave is a slight peak due to elevation and closure of the tricuspid valve at the onset of ventricular systole. The third or "v" wave mirrors the rise in pressure in the right atrium as it fills during the end of ventricular systole and early part of diastole before the tricuspid valve opens. Between the "c" and "v" peaks, i.e., throughout most of systole, the jugular vein empties completely and venous tracings show a pronounced depression or negative wave, termed "x." Because this venous collapse is the most striking feature of the normal pulse, the latter is referred to as a *negative venous pulse*. The "x" depression in systole is due to the aspirat-

ing effect on the blood in the veins when the tricuspid valve is drawn down toward the apex and blood is expelled from the thoracic cavity during systole.

In *tricuspid insufficiency,* the right atrium is never completely emptied and there is an elevated pressure. In addition blood is regurgitated into this chamber during ventricular systole. As a result of the persistent atrial stasis and the impulse of the regurgitant stream, the cervical veins remain filled and expand during systole. The negative wave or depression "x" disappears. This results in the so-called *positive venous pulse* or *ventricular venous pulse* of tricuspid insufficiency. It is often visible, without the aid of tracings, as a broad systolic wave ascending the neck along the course of the internal jugular vein up to the very ear lobe. The external jugular vein may be too distended to disclose pulsation.

A positive venous pulse may be insignificant in tricuspid insufficiency if the right atrium is greatly dilated and the regurgitant stream has little effect on its large content. On the other hand, a positive venous pulse may be observed in the absence of tricuspid insufficiency when there is atrial fibrillation with right heart failure and advanced venous stasis. But the systolic pulsation is rarely as well defined as in tricuspid insufficiency.

Atrial Venous Pulsation in Tricuspid Stenosis. In tricuspid stenosis the cervical venous pulse often shows an accentuated "a" wave due to the increased force of contraction of the hypertrophied right atrium. In addition the obstruction at the tricuspid orifice may cause a regurgitation of blood from the right atrium into the cervical veins. These factors cause a rise in venous pressure and a consequent venous pulsation during atrial systole. This is known as the *auricular venous pulse,* and is a characteristic feature of tricuspid stenosis. But it may occur if there is pronounced left atrial hypertrophy with a large interatrial septal defect. It may be absent if the atria are fibrillating or when the right atrium is so dilated that its contraction is relatively abortive.

Sometimes there is a distinctly visible *double* pulsation of the cervical veins, one synchronous with ventricular systole and one presystolic in time. The latter denotes tricuspid stenosis and the former concomitant insufficiency or pronounced right atrial stasis behind the tricuspid obstruction. I have also observed distinct double jugular venous pulsations in a case of rupture of a congenital aneurysm of the sinus of Valsalva into the right atrium.

Systolic (Ventricular) and Atrial Liver Pulse. In cases of tricuspid insufficiency there is usually a palpable pulsation of the liver during ventricular systole.[45] It is explained by regurgitation of blood from the right ventricle into the atrium. This leads to a transmitted pulse into the inferior vena cava, hepatic veins and their tributaries, corresponding to the systolic jugular pulse.

Clinically the systolic liver pulse is best noted as an expansile sensation when the liver is examined bimanually, one palm being held over the posterolateral surface of the lower right axilla and the other anteriorly over the right upper quadrant of the abdomen, i.e., over the liver. This pulsation must be differentiated from the pulsations of a large right ventricle transmitted through the diaphragm or from similar transmitted pulsations from a dynamic or aneurysmal abdominal aorta. But these pulsations are rarely expansile and strike only one of the two examining hands. A systolic liver pulse may be absent in tricuspid insufficiency if the regurgitant flow is too slight, if there is a hugely dilated right atrium or if longstanding passive congestion has produced a pseudocirrhotic liver which cannot pulsate.

Rarely a systolic pulsation of the spleen has been described in tricuspid insufficiency.[37]

In *tricuspid stenosis* there may be a *presystolic* or *atrial liver pulse* corresponding to the *atrial venous pulse* and due to a similar mechanism. This is best demonstrated by graphic registration but may be recognized occasionally by bimanual palpation. A double liver pulse may be encountered when there is a combination of tricuspid stenosis and insufficiency, one pulsation being due to atrial contraction and the other to ventricular systole, which causes a regurgitant impulse in the right atrium and inferior vena caval tributaries.

The Heart in Tricuspid Valvular Disease. The physical signs over the heart are often determined by the associated mitral stenosis or other valvular disease.

In cases of *tricuspid insufficiency* there may be a characteristic see-saw movement of the chest wall.[22, 9] This is due to a propulsion of the lower right side of the sternal region by the pulsating liver, while simultaneously ventricular systole causes a pronounced depression of the precordium. The latter is due to the aspiratory effect on the chest wall of ventricular ejection of blood out of the thorax while the influx of blood into the heart is prevented by the regurgitant stream.

Percussion reveals enlargement of the heart, especially to the right. In cases of pronounced tricuspid stenosis the dilated and hypertrophied right atrium may occasionally cause the right border to reach the right midclavicular line.

Auscultatory findings are usually those of mitral stenosis or of mitral and aortic disease, unless the tricuspid insufficiency is functional in origin. The tricuspid lesion itself may produce a systolic murmur over the lower end of the sternum or adjacent to it. In cases of tricuspid stenosis a diastolic or presystolic rumbling murmur may be heard in the same location. When the murmur is loud, it may be accompanied by a thrill. Occasionally an accentuated second pulmonic sound, present in cases of mitral stenosis or pulmonary hypertension due to pulmonary disease, becomes soft with the development of tricuspid insufficiency.

A *reversal of the parodoxical pulse* may be observed in cases of tricuspid insufficiency. Instead of the slight reduction in pulse volume with deep inspiration felt normally or the pronounced reduction associated with constrictive pericarditis (pulsus parodoxus), there is an increased pulse amplitude with deep inspiration and a diminution with expiration. For the pulmonary vascular capacity increases little during inspiration, while the venous return and therefore the cardiac output are significantly augmented.

Roentgen Ray Examination of the Heart. The enlarged right atrium produces a widening of the transverse diameter of the heart. The right lower cardiac contour is displaced to the right. In the right oblique position the enlarged right atrium encroaches on the most caudad portion of the right retrocardiac space. Even though mitral stenosis is present, the enlarged right atrium may displace the barium-containing esophagus to the left. The combination of left atrial enlargement due to mitral stenosis and of right atrial enlargement due to tricuspid stenosis may produce double atrial concentric contours on the right side of the cardiac silhouette.

In cases of pronounced tricuspid insufficiency, with or without stenosis, the right ventricle as well as the right atrium is enlarged and the heart has a globular triangular or transverse configuration. The size and shape of the left contours are determined by associated mitral and aortic disease.

Two features are distinctive of tricuspid valvular disease: (1) The pulmonary fields are surprisingly clear despite the clinical features of heart failure. This contrasts with the congestion observed in heart failure due to mitral stenosis, uncomplicated by tricuspid disease. (2) Secondly, the vascular shadow of the superior vena cava is widened and pulsates in systole or presystole. The right innominate vein may also appear prominent and may pulsate. Occasionally also there is widening and pulsation of the left innominate vein below the medial end of the left clavicle. The diaphragm may be elevated in systole by the pulsating liver when normally it is depressed.

The *electrocardiogram* is usually characterized by right axis deviation, by inversion of the T_3 and often also of T_2. Particularly in tricuspid stenosis there may be wide, notched and high voltage P waves when there is sinus rhythm. A diphasic P wave in right precordial leads has been described by Ellis and Brown[12] as distinctive of tricuspid disease, but it may occur with mitral stenosis alone. A delayed onset of the intrinsic deflection in V_1 and V_2 of more than 0.04 second has been observed in the majority of cases of tricuspid disease and may be of diagnostic help.[2] Auricular fibrillation occurs commonly. Tricuspid stenosis with nodal tachycardia and atrioventricular dissociation has been reported.[13]

Diagnosis

Tricuspid disease should be suggested by the presence of a large pulsating liver and positive venous pulse in a patient with systemic venous congestion, cyanosis, ascites and valvular heart disease. A characteristic bluish yellow facies, due to combined cyanosis and mild icterus, in a patient with mitral stenosis should suggest the association of tricuspid disease. Evidence of pronounced right heart failure without orthopnea or paroxysmal dyspnea should also suggest this diagnosis. Prolonged venous congestion with hepatomegaly and recurrent ascites out of proportion to edema, in a patient with mitral stenosis who has had seemingly adequate treatment, usually denotes organic tricuspid disease.

Confirmation of the diagnosis may be provided by the following: (1) A systolic murmur over the xiphoid process in tricuspid insufficiency or a presystolic murmur in tricuspid stenosis, provided these murmurs can be distinguished from those of the associated mitral disease, (2) graphic demonstration of a systolic liver pulse and a positive jugular venous pulse in cases of tricuspid insufficiency, or of an atrial or double liver pulse and atrial jugular venous pulse in tricuspid stenosis, (3) prominent enlargement of the right atrium in addition to changes due to associated cardiovalvular disease, (4) roentgen ray evidence of clear pulmonary fields with widened pulsating venae cavae.

Differentiation of organic from functional tricuspid insufficiency is difficult, but the latter usually disappears with active treatment of the congestive heart failure.

Constrictive pericarditis most closely simulates tricuspid valvular disease but the heart is not enlarged and evidence of organic cardiovalvular disease is absent in the former.

Congenital atrial septal defect with mitral stenosis does not produce a distinct liver pulsation, and is often associated with large pulsating hilar vessels.

Cirrhosis of the liver is excluded by the presence of venous engorgement in the superior as well as the inferior vena caval tributaries.

Course and Prognosis

Patients with organic tricuspid valvular disease are often ambulant and experience relatively long periods of comfort despite venous engorgement, hepatic enlargement and ascites.

The comfort, which is due to the absence of orthopnea and paroxysmal dyspnea, is only relative because activity is greatly limited and the patient must lead a life of semi-invalidism or invalidism. The manifestations of heart failure persist substantially longer in cases of tricuspid disease than in those of isolated mitral stenosis or of mitral and aortic disease. On the other hand the general outlook for organic tricuspid disease is less favorable than for other valvular disease in that heart failure and death occur at a much earlier age.[42] Organic tricuspid stenosis and insufficiency are almost always combined with mitral and aortic valvular disease and indicate, as a rule, more severe and more extensive rheumatic inflammation than in cases of mitral and aortic disease alone. This may account for the poorer prognosis in the former. Death in tricuspid valvular disease eventually results from progressive right heart failure, pulmonary embolism and infarction, active rheumatic fever or bronchopulmonary infection.

The outlook in cases of functional tricuspid insufficiency depends on the underlying disease responsible for the right heart failure. Most often, functional tricuspid insufficiency denotes the end stage of chronic valvular or pulmonary disease and is therefore of ominous significance. But temporary improvement and disappearance of the valvular insufficiency occur frequently with adequate therapy.

Treatment

The treatment is that of the underlying disease and of advanced right heart failure (Chapter 9). Bed rest, extreme restriction of sodium intake, digitalization and the administration of mercurial diuretics are the cardinal therapeutic measures. With adequate diuresis, abdominal paracenteses to remove ascitic fluid may not be required. Sometimes, however, this procedure must be repeated many times over a period of years in order to afford symptomatic relief. Thoracentesis affords relief when a large hydrothorax is responsible for dyspnea.

PULMONARY INSUFFICIENCY

Etiology and Pathology

Organic insufficiency of the pulmonary valve is very rare.[44] A relative or functional insufficiency is probably not uncommon, but statistics as to its occurrence are extremely varied and unreliable.[5] Pulmonary insufficiency may be classified as *acquired* and *congenital*, and the acquired lesions may be further subdivided into the *organic* and *functional* varieties. The following causes of pulmonic insufficiency have been noted:

I. Acquired pulmonary insufficiency
   A. Organic
      1. Bacterial endocarditis
      2. Rheumatic fever
      3. Pulmonary arteritis and valvulitis secondary to aortic aneurysm
      4. Syphilis of the pulmonary artery

B. Functional (pulmonary hypertension)
   1. Mitral stenosis
   2. Bronchopulmonary disease
   3. Primary pulmonary sclerosis

II. Congenital pulmonary insufficiency
   A. Deficient or supernumerary pulmonic cusps
   B. Congenital dilatation of the pulmonary artery

Acquired Organic Pulmonary Insufficiency. The commonest cause is a bacterial endocarditis involving the pulmonic valve. Of 119 cases of pulmonic insufficiency taken from the literature and the autopsy records of Guy's Hospital, Pitt[28] found that 60 were due to a bacterial endocarditis. Insufficiency results from improper closure of the valves because of the attached vegetations or because of destruction or perforation of a cusp. Multiple bacterial pulmonary emboli may arise from the vegetations. Thayer[41] has noted the relative frequency with which the gonococcus attacks this valve, and a similar tendency has been noted for the pneumococcus. Bacterial endocarditis of the pulmonic valve is usually an isolated valvular lesion. Of 26 cases, Langeron and Gardère[23] found that the bacterial vegetations were confined to the pulmonic valve in 21, and associated with bacterial endocarditis of other valves in 5.

McGuire and McNamara[25] recently reported 3 cases of rheumatic pulmonary insufficiency, one of them with slight pulmonic stenosis. In all three cases, the other valves were simultaneously affected. I have occasionally seen gross rheumatic vegetations on the pulmonic cusps as well as mild microscopic inflammatory lesions of the valve and valve ring. But except for slight thickening of these cusps, I have never seen rheumatic valvular deformity of sufficient degree to interfere with their function.

Occasionally a pulmonic insufficiency arises from pressure of an aortic aneurysm on the pulmonary artery at or just above the level of the pulmonary cusps, especially the left cusp. Inflammation of the pulmonary artery and cusp results from the pressure of contact or from perforation of the aneurysm. The cusp subsequently becomes adherent to the arterial wall so that it can no longer aid in closing the pulmonic orifice.

Syphilis of the pulmonary artery has been recorded in 66 cases, but according to Brenner[7] the diagnosis is established in only 15. This may produce pulmonic insufficiency by dilatation or aneurysm of the main vessel with concomitant dilatation of the pulmonic ring, or by a widening of the commissure similar to that in luetic aortic insufficiency.

Many of the cases of pulmonc stenosis are accompanied by auscultatory or anatomic evidences of insufficiency.

Functional Pulmonic Insufficiency. The pulmonic valve becomes relatively insufficient when the pulmonic ring becomes dilated. Functional or relative pulmonic insufficiency has been known also as the insufficiency of high pressure in the pulmonary artery. The pulmonary hypertension is caused presumably by resistance to blood flow due to mitral valvular obstruction (p. 579), long-standing disease of the lungs, or narrowing of the small pulmonary arteries and arterioles.

Congenital Pulmonary Insufficiency. Pulmonary insufficiency may be caused by two types of congenital defect, namely, *dilatation of the pulmonary artery* and *abnormality in the number of pulmonic cusps*. In 1000 cases of congenital

heart disease studied by Abbott,[1] there were 8 primary cases of pulmonary insufficiency, 2 of which were due to valvular abnormalities and 6 to congenital dilatation of the pulmonary artery. There were 13 additional cases, in which the pulmonic insufficiency was associated with other congenital defects of the heart. Kissin[21] recently noted that there were reports of 151 hearts with four pulmonic cusps, but in only 3 of these cases was there sufficient functional disturbance to produce clinical signs. Insufficiency occurs despite the supernumerary cusp because the pulmonary artery and ring are greatly dilated. Dilatation of the pulmonary artery may occur as a primary solitary defect or in association with other major defects. Oppenheimer[26] reported 8 cases of idiopathic dilatation of the pulmonary artery and its branches, in 4 of which there was evidence of pulmonary insufficiency.

The Heart

Two of the features common to all the varieties of pulmonic insufficiency are (1) hypertrophy of the right ventricle, and (2) regurgitation of blood from the pulmonary artery into the right ventricle, with the consequent production of a diastolic murmur. In many cases there is also (3) a considerable dilatation of the pulmonary artery, the normal circumference of 6 to 8.5 cm. being exceeded in varying degree. Dilatation and hypertrophy of the right ventricle may develop as a consequence of the regurgitation of blood and may represent a compensatory phenomenon similar to that of the enlarged left ventricle in aortic insufficiency. Right ventricular hypertrophy with relatively little dilatation may, however, have preceded the onset of pulmonary insufficiency due to the increased resistance of pulmonary hypertension in chronic pulmonary disease. This mechanism corresponds to the development of left ventricular hypertrophy in systemic hypertension.

Symptomatology

The symptomatology[31, 5] is usually overshadowed by the primary disease of which the pulmonic insufficiency is a mere incident. Thus dyspnea on exertion, cough, mild or intense cyanosis, hemoptysis, somnolence, peripheral edema and ascites may also be attributed to the underlying pulmonary, valvular or congenital heart disease, independent of the pulmonary insufficiency.

The cases with congenital dilatation of the pulmonary artery may be asymptomatic and discovered only on routine fluoroscopy. Dyspnea is a frequent symptom. Cyanosis is usually present and may be intense. Polycythemia of moderate degree is observed in the cyanotic patients. Cough also is relatively frequent but not severe.

Examination of the Heart

Physical examination of the heart reveals the abnormalities due to the associated cardiac disease as well as those of pulmonary insufficiency. The dilated pulmonary artery causes dullness in the second and third left interspace and occasionally a pulsation in this area. The diagnostic sign is a soft or loud, blowing or harsh diastolic murmur in the second or third left interspace. In cases of mitral stenosis, this has been termed the Graham-Steell[36] murmur (p. 579). There is often an associated systolic murmur attributed to eddies in the dilated pulmonary artery. The second pulmonic sound may be accentuated,

due to the increased pressure in the pulmonary artery and closer approximation of the dilated artery to the chest wall.

Roentgen ray examination discloses evidence of right ventricular hypertrophy (p. 29) and of the dilatation of the pulmonary artery.[32] The hilar shadows may be prominent and even so large as to be mistaken for mediastinal tumors, e.g., in the cases of congenital or idiopathic dilatation of the pulmonary artery.[35] Often there is a distinct pulsation of the pulmonary artery. Prominent pulsations of the hilar vessels have been described as "hilum dance."[27]

The electrocardiogram is that observed with right ventricular hypertrophy (p. 41).

Diagnosis

The diagnosis depends on the discovery of a pulmonic diastolic murmur and right ventricular hypertrophy, and on the absence of left ventricular enlargement or the peripheral circulatory phenomena of aortic insufficiency. The diagnosis may be suggested on roentgenologic examination by the finding of a large right ventricle and large pulsating pulmonary arteries.

Prognosis and Treatment

These are determined by the underlying or associated disease.

PULMONIC STENOSIS

Pulmonic stenosis is almost exclusively a congenital lesion and is discussed in the chapter on congenital heart disease. Acquired pulmonic stenosis is extremely rare, especially as a clinically significant lesion. There may be a true stenosis due to inflammation and adhesion of the valves, or a functional stenosis incidental to other diseases.

Acquired organic stenosis of the pulmonary valve has been attributed to rheumatic valvulitis, bacterial endocarditis and to trauma. All are very rare. Rheumatic inflammation may be engrafted on a congenital bicuspid pulmonic valve.[33] In the case of McGuire and McNamara,[25] rheumatic pulmonic stenosis and insufficiency were associated with stenosis of the other three valves. The stenotic adherent cusps form a single protruding diaphragm or dome pierced at its center by a small opening.

Functional pulmonic stenosis results from obstruction of the pulmonary orifice by massive bacterial valvular vegetations and by large emboli extending from the right ventricle into the pulmonary artery. I have seen both of these conditions, characterized by the sudden development of a loud, harsh systolic murmur and a systolic thrill over the pulmonic area. Litten[24] has reported pulmonic stenosis due to the plugging of the pulmonary artery by echinococcus cysts. Pulmonic stenosis may also be caused by the pressure of tumors, mediastinal glands or of an aortic aneurysm on the pulmonary artery at or near the level of the valves.

There is hypertrophy and dilatation of the right ventricle; when the right ventricle fails, the right atrium may also become dilated and hypertrophied. The left chambers are normal unless there is associated disease of the mitral and aortic valves.

A prominent feature is the frequency of pulmonary tuberculosis. The pulmonary artery is usually dilated beyond the stenotic site, possibly because of atrophy of its wall.

Clinical Features

The clinical features of congenital pulmonic stenosis are discussed in the chapter on congenital heart disease (p. 675). The clinical features of the rare instances of acquired pulmonic stenosis are usually determined by the underlying bacterial endocarditis, neoplasm, embolism or other causative or associated disease. In cases of rheumatic pulmonic stenosis the clinical manifestations are usually determined by the more severe lesions of the other valves.

The *diagnostic signs* due to the pulmonic stenosis per se are the loud rough systolic murmur in the second or third left interspace, the palpable thrill in the same area, the weak or absent second pulmonic sound, the roentgenologic and electrocardiographic evidence of enlargement of the right ventricle (coeur en sabot) and prominence of the pulmonary artery salient.

COMBINED VALVULAR DISEASE

For didactic reasons the individual valvular lesions have been described separately. As a rule multiple valves are the site of significant lesions due to rheumatic fever. Mitral stenosis and aortic insufficiency or stenosis occur most commonly. Occasionally organic tricuspid stenosis and insufficiency coexist while significant disease of all four valves is rare. Functional tricuspid insufficiency is not uncommon in the late stages of combined mitral and aortic disease.

The clinical picture, including the physical and roentgenologic signs, is usually determined by the relative severity of the individual lesions and by their order of development. As a rule each lesion produces its own characteristic effects on individual cardiac chambers and its own physical and roentgenologic signs which permit recognition of the multiple lesions. Therefore it is unnecessary to devote separate discussions to the various combinations of valvular lesions.

In some instances one valvular lesion may relieve the strain, or partially neutralize the effects of another. Accordingly, various modifications in prognosis have been attributed to the different combinations of valvular disease However, such attempted correlations are untenable because other factors, such as rheumatic activity, severity and extent of myocardial damage and the development and severity of complicating coronary arteriosclerosis, are extremely important in determining the course and prognosis of rheumatic cardiovalvular disease.

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PART V

ETIOLOGIC FORMS OF HEART DISEASE

30

CONGENITAL HEART DISEASE

Despite the epochal contributions of Peacock,[154] Rokitansky[176] and Vierordt,[205] the subject of congenital heart disease long remained an academic study. This was due both to the rarity with which an accurate diagnosis of the lesion could be made and to the inability either to prevent its occurrence or to remedy it. In recent years the scholarly clinical-pathologic contributions of Maude Abbott[1] and of Laubry and Pezzi[118] have lent a fruitful stimulus which has resulted in the development of great accuracy in the diagnosis of the exact congenital cardiac lesions or at least of the major defect present in a given case. The recent utilization of contrast media to portray roentgenographically the individual portions of the heart and great vessels[168, 194] has enhanced our diagnostic accuracy in this field. The employment of intracardiac catheterization to determine the oxygen content and pressure within various cardiac chambers and to determine cardiac output and pulmonary blood flow has provided additional diagnostic data.[18, 19, 51, 188, 50] The subject of congenital heart disease is now squarely within the domain of the clinical cardiologist; great surprises at the pathologist's table should become uncommon as regards cardiac anomalies. At the same time, amazing progress has been achieved in the surgical treatment of certain congenital cardiovascular anomalies and these advances enhance the importance of diagnostic accuracy.

INCIDENCE

The incidence of congenital cardiac abnormalities is still uncertain and varies in the different age groups. According to most reports, major congenital cardiac anomalies are found in 0.5 to 2 per cent of autopsied cases of organic heart disease. In the series reported by Jacobius and Moore[105] from the New York Hospital the incidence was 8.1 per cent. Among adults, it is improbable that congenital heart disease forms more than a fraction of 1 per cent of the cases of clinical heart disease. On the other hand, among school children with cardiac ailments the incidence of congenital heart disease was reported to be 11 per cent and among children above the age of two, 14 per cent.[215] Below the age of five the vast majority of cases of heart disease are of congenital origin since rheumatic fever is very uncommon in children before this age. For this reason, the diagnostic importance of determining whether a cardiac lesion was present in infancy or early childhood is obvious.

ETIOLOGY

Basic Cause. Congenital anomalies of the heart and great vessels are due to *arrested or defective prenatal development.* But it is uncertain whether intrinsic factors in the germ plasm or extrinsic factors in the embryo's environment are of major importance.[52] Disease of the fetal envelopes, amniotic adhesions or other mechanical disturbances in the environment of the embryo may interfere with that perfection and symmetry of growth which is essential for the normal development of the heart and great vessels. That this is the chief causative factor is indicated by the frequent association of other congenital anomalies elsewhere in the body of subjects with cardiac defects and by the occurrence of cardiac anomalies in siblings. In some cases the origin of defective development of the heart may be situated in the germ plasma rather than in the environment of the embryo. This is indicated by evidence of hereditary factors, but in the great majority of cases the role of heredity is insignificant.

Much of the evidence that disturbances of development (whether due to fetal environment or defective germ plasm) account for congenital cardiac disease is based on a correlation of the lesions observed in human hearts with a phylogenetic study of the structures in the hearts of lower forms, including the reptiles, amphibians and fishes. Notable contributions have been made by Rokitansky[176] with respect to septal lesions, by Keith[110] on the abnormal development of the bulbus cordis and by Spitzer[189] on the transposition of the great vessels. These will be discussed under general embryology and embryology of the individual lesions.

Associated Anomalies. The likelihood that congenital cardiac anomalies are due to disturbances in the embryo's environment is supported by the frequency of anomalies in other parts of the body in the same subjects; for it is to be anticipated that defects in the localized milieu surrounding the embryo would disturb not only the development of the heart but also that of other structures. Vierordt[205] observed associated anomalies in 80 of 700 cases (11 per cent) of congenital heart disease, Abbott[1] in 188 of 1000 cases (18.8 per cent). Keith[110] found cardiac anomalies in 14 of 23 malformed fetuses.

While some of the associated anomalies are of a hereditary nature (see below), most of them are not, and therefore point to the presence of abnormalities in the fetal environment. Mongolian idiocy occurs rather frequently. Thomson[203] noted congenital heart disease in 50 of 300 cases (17 per cent) and von Höfe[206] in 14 of 150 cases (9 per cent) of mongolian idiocy. Conversely, Morse[143] found 6 Mongolian idiots in 100 cases of congenital heart disease and Irvine-Jones[104] 7 in her 100 cases. The cardiac defect most often associated with Mongolian idiocy is either a complete absence of the interauricular septum, a persistent common atrioventricular canal or a persistent ostium primum (p. 642, defect in the lower portion of the auricular septum). There are often accessory spleens or the spleen is absent.

Heredity. The possibility that defects of the germ plasm account for at least some cases of congenital heart disease is indicated by the following evidences of the role of heredity: (1) There are associated anomalies which are generally recognized as being of a hereditary nature. These include polydactylism, clubbed foot, fetal lobulation of the kidneys and congenital dislocation of the hip. (2) There is occasionally an ancestral history of congenital heart disease. (3) Cardiac defects have been reported in identical twins. (4) There are

records of families with multiple instances of similar or identical congenital cardiac anomalies in more than one generation.[207]

Virus and Other Infections. The occurrence of rubella (German measles) in the first two or three months of pregnancy has been associated with a significant incidence of congenital cataracts and cardiac anomalies in the offspring.[84, 195, 4, 8] This may be related to the fact that the entire development of the heart and great vessels is completed in the first two months of embryonic life. It is important to determine whether the association of maternal rubella and congenital heart disease is common or rare[71] in order to evaluate the recommendation that pregnancy be interrupted with the occurrence of rubella in the first trimester of pregnancy.

The above observations suggest the possibility that other maternal and fetal infections may be responsible for congenital heart disease. Fetal endomyocarditis[89] and syphilitic myocarditis have been reported as the cause in occasional cases.

Nutrition. Vitamin Deficiencies. Animal experiments suggest that dietary deficiencies in the mother may result in congenital malformations.[210] But there is no significant evidence of such a relationship between vitamin or other nutritional deficiencies and the occurrence of congenital heart disease in man.

Sex. If all forms of congenital cardiac lesions are considered, the incidence of congenital heart disease is almost equally divided between the sexes. However, certain individual lesions occur with predilection for one sex or the other. Thus, coarctation of the aorta (3:1), anomalies of the semilunar cusps (5:1), defects of the aortic septum and transposition of the great vessels (2:1 or 3:1) are more frequent among males while patency of the ductus arteriosus (Botalli) occurs more commonly in females (2 or 3:1).

GENERAL EMBRYOLOGY AND PATHOLOGY

In its prenatal development the human heart passes through a series of stages whereby a simple cardiac tube is transformed into four distinct chambers separated by septa and valves and leading into the aorta and pulmonary artery. An important effect of this development is the separation of the systemic circulation from that in the lungs. The original simple tube is fixed at two points, the arterial or cephalic end and the venous or caudal end. As the heart grows, this tube elongates, and since its ends are fixed, it bulges and twists in a spiral fashion so as to assume an **S** shape. This so-called torsion is normally clockwise at the arterial and counterclockwise at the venous end. By the fourth week (3 mm. embryo), the heart is differentiated into a successive series of four chambers which from the venous to the arterial end are: (1) the sinus venosus which receives the vitello-umbilical veins and the ducts of Cuvier (later the superior vena cava and coronary sinus), (2) the atrium, (3) the ventricle, and (4) the bulbus cordis from which the primitive truncus arteriosus (later the aorta and pulmonary artery) arises.

Most of the congenital cardiac disturbances arise between the fifth and eighth weeks of embryonic life. During this time the atrium and ventricle are each divided by a septum into two chambers, the atrioventricular canal is divided by a septum into left and right segments, the atria are separated from the ventricles by valves and the primitive truncus arteriosus is divided into the aorta and pulmonary artery which lead respectively from the left and right ventricles. Details concerning the embryologic basis of the various congenital

cardiac lesions will be presented in the discussion of the individual anomalies.

In most cases of congenital heart disease, the lesions are not isolated, two or more lesions being present in the same subject. The frequency of combined lesions is due in many instances to simultaneous maldevelopment of two different structures in the heart which are in close anatomic juxtaposition. Thus proper closure of the upper part of the ventricular septum requires normal development of the aorta and pulmonary artery and the septum between them. Hence ventricular septal defects are frequently associated with dextraposition of the aorta and pulmonary stenosis or atresia. In other cases a primary lesion produces changes in pressure in the chambers of the heart or great vessels so that fetal openings do not close as they normally should. A patent foramen ovale or ductus arteriosus may result secondarily from atresia or stenosis of a valvular orifice, or transposition of the great vessels, and this patency may be a compensatory lesion to maintain a continuous circulation. In other cases, a combination of lesions represents simultaneous disturbance in multiple unrelated portions of the heart.

Classification of Congenital Cardiac Lesions

The classification used here is based on the major pathologic defect, which in turn is dependent on a specific embryologic disturbance. Since many of the commoner lesions are associated with distinctive clinical or roentgenologic features, this classification has the practical advantage of facilitating diagnosis. The lesions considered in some detail are interatrial (atrial) septal defects, interventricular (ventricular) septal defects, dextraposition or transposition of the great vessels, patency of the ductus arteriosus, coarctation of the aorta, pulmonary stenosis and right-sided aortic arch. Certain combinations of lesions occur with sufficient frequency and produce a distinct enough clinical picture to warrant their being learned as clinical-pathologic entities. This applies to the tetralogy of Fallot and the combination of an auricular septal defect with mitral stenosis.

Congenital heart disease has been classified by Abbott[1] into three groups, an acyanotic, a potentially cyanotic and a persistently cyanotic, the latter being subdivided according to the intensity of the cyanosis. This classification is unique in that it is based on the presence or absence of a single nonspecific symptom. It seems preferable, in the absence of a specific etiology, to classify the cases of congenital heart disease according to pathologic anatomic defects. The presence or absence of cyanosis, in addition to many other clinical features, is useful in differential diagnosis.

GENERAL SYMPTOMATOLOGY

Certain congenital anomalies are of no clinical importance since they produce neither subjective symptoms, physical signs nor other objective abnormalities. These include bifid apex of the heart, persistent left superior vena cava, and most instances of patent foramen ovale and of anomalous septa and chordae. Other anomalies produce neither symptoms nor signs but are the site of serious complications, e. g., a bicuspid aortic valve is often complicated by bacterial endocarditis. In cases of pure dextrocardia with situs inversus there are no symptoms nor physical signs but the roentgenoscopic and electrocardiographic examinations reveal a characteristic picture.

Another group of lesions may produce no subjective symptoms for many

years, but distinctive physical, roentgenologic and electrocardiographic signs are associated. There are usually *cardiac murmurs* which may be typical in location and character and associated with palpable *thrills*. There are often also *changes in the size and shape of the cardiac silhouette*. There may also be *abnormalities in blood pressure,* as in cases of coarctation of the aorta, or patent ductus arteriosus. The latter may be associated with altered circulatory dynamics similar to those in cases of free aortic insufficiency.

Subjective symptoms appear as a rule only with a diminution of the cardiac reserve or the development of frank cardiac failure. These are identical with the symptoms of congestive heart failure due to other etiologic types of heart disease. *Dyspnea on exertion* is the commonest symptom and often appears early in the course of the disease. A striking form of dyspnea is that which appears in paroxysms and is usually associated with an intensification of cyanosis. In many cases exertional dyspnea is secondary to pulmonary congestion associated with left-sided heart failure. Often, however, the dyspnea appears to be due to excessive arterial oxygen unsaturation especially following exercise, with consequent anoxia of the carotid sinus and respiratory center.

Cough complicates dyspnea when the latter is due to pulmonary congestion, but both dyspnea and cough may be due to tracheal compression by a double aortic arch or aberrant vessel. Congestion of the abdominal viscera, with digestive disturbances, hepatic enlargement and ascites and peripheral edema, results from failure of the right side of the heart. Excessive fatigability and weakness are relatively common.

Cerebral symptoms including faintness, dizziness, headache, and more rarely syncope, convulsions, delirium, paralyses and coma are observed occasionally, especially in patients with cyanosis. These symptoms are due partly to cerebral anoxia (arterial anoxemia) and partly to the polycythemia with consequent circulatory stasis or complicating cerebral thromboses or hemorrhage. But cerebral symptoms may also be due to inadequate cerebral blood flow in cases of aortic or subaortic stenosis, to cerebral embolization in complicating bacterial endocarditis or endarteritis, to ruptured cerebral embolism in coarctation of the aorta, or to cerebral abscess in cases of septal defects and paradoxic embolism. Adams-Stokes attacks may occur in cases of congenital heart block.

Vascular disturbances in the extremities including coldness, numbness and tingling or pain may appear in patients with or without cyanosis and polycythemia. These symptoms as well as intermittent claudication are not uncommon in cases with the adult type of coarctation of the aorta. Malnutrition and underdevelopment may result from deficient peripheral blood supply. Special symptoms may be identified with individual lesions. Thus, the pressure of a dilated pulmonary artery, a persistent right aortic arch or of an anomalous vessel on the esophagus, trachea or recurrent laryngeal nerve may cause dysphagia, dyspnea or hoarseness, respectively.

The detailed cardiac signs and other features associated with congenital heart disease are best discussed below with the important individual cardiac anomalies.

The symptoms usually attributed to congenital heart disease are *cyanosis* and *clubbed fingers*. But it is erroneous to believe that these are characteristic of the majority of cases. The diagnosis will usually be overlooked if it depends on the discovery of these manifestations, since in most cases cyanosis is absent

or occurs only as a terminal event. Cyanosis of varying intensity was encountered in 351 of Abbott's[1] 1000 cases and in 124 others it appeared terminally. Since cyanosis is almost always associated with the severe multiple cardiac anomalies which lead to death in infancy or very early childhood, this symptom is much less common than indicated by the above figures if only cases above the age of three are considered.

The cyanosis is most marked in the lips, tips of fingers or toes, nose, ears and mucous membranes, but it may be generalized. In cases of interruption of the aortic isthmus, cyanosis is limited to the lower extremities; if atresia of the aortic isthmus is combined with transposition of the great vessels, there is more intense cyanosis of the head and upper extremities than in the lower. A distinct cyanosis may be observed in the retina (cyanosis retinae). The optic disc is usually congested. The veins are congested, purplish-red and tortuous. Retinal hemorrhages, suffusion of the conjunctiva and rarely exophthalmos may be associated. Clubbing of the fingers and toes was noted in 132 of Abbott's[1] 1000 cases. It usually appears later than cyanosis in any given case, time being an important factor in its development. For the pathogenesis of cyanosis and clubbed fingers in congenital heart disease, see below.

A secondary *polycythemia* occurs frequently in the cases with cyanosis. This appears to compensate for the oxygen unsaturation of the blood. The red blood count in such cases usually varies between 6 and 7 millions per cu. mm. More marked polycythemia is observed in association with intense, persistent cyanosis. Occasionally there are 10 to 12 million red blood cells per cu. mm. The hemoglobin is correspondingly elevated to 110 to 130 per cent in the patient with moderate cyanosis and occasionally reaches 150 to 200 per cent with extreme polycythemia. An *increase in blood volume* and *blood viscosity* is associated with polycythemia. The *hematocrit* usually exceeds 55 per cent.

Pathogenesis of Cyanosis in Congenital Heart Disease

Cyanosis appears in cases of congenital heart disease when there is more than 5 gm. of reduced hemoglobin per 100 cc. of blood. This corresponds approximately to an oxygen unsaturation of 6.5 volumes per cent in the capillary blood. In terms of arterial blood, cyanosis appears when the oxygen saturation $\left(\frac{\text{oxygen content}}{\text{oxygen capacity}}\right)$ is approximately less than 75 per cent. This or higher degrees of oxygen unsaturation result from (1) the admixture of oxygenated with venous blood due to an abnormal communication between the left and right sides of the heart or between the aorta and pulmonary artery, (2) deficient pulmonary blood flow and pulmonary aeration, (3) peripheral capillary stasis with increased deoxygenation in advanced congestive heart failure and in polycythemia. Accessory factors in the production of cyanosis have already been discussed in detail (p. 123).

In the absence of cardiac failure, many cases of congenital heart disease never present cyanosis for there is no venous-arterial shunt. This group includes the cases of adult coarctation of the aorta, pure mitral, aortic or subaortic stenosis, uncomplicated dextrocardia, uncomplicated bicuspid or quadricuspid semilunar valves, persistent right aortic arch, and many anomalies of the coronary or pulmonary arteries and of the pericardium.

In cases with an abnormal communication between the left and right sides of the heart or great vessels, cyanosis is absent if the flow is from the left to the

right or from the aorta to the pulmonary artery. Thus patients with a patent ductus arteriosus (Botalli), a patent foramen ovale, or an uncomplicated auricular, ventricular or aortic septal defect are usually free from cyanosis because the pressure in the arterial circuit (aorta and left side of the heart) is normally higher than that in the venous circuit and therefore the venous blood does not contaminate the arterial. However, cyanosis may appear sporadically or terminally (cyanose tardive) in these cases if the pressure on the venous side is elevated sufficiently to reverse the flow through the abnormal communication and thus produce a venous-arterial shunt. This may result from exercise, and in infants from crying or sucking due to an increased venous return to and an elevation of pressure in the right side of the heart. Certain pathologic conditions, especially pneumonia and other bronchopulmonary disease and cardiac failure, may also cause cyanosis by elevating the pressure in the right chambers of the heart, thus causing a reversal of flow through the arteriovenous shunt.

In a third group of cases cyanosis usually is present throughout most of the course of the disease. In these cases the flow of blood through the abnormal shunt is constantly from the venous to the arterial side because some associated lesion has caused the pressure on the right or venous side to exceed that on the left side of the heart and aorta. In some congenital cardiac lesions, such as complete transposition of the great vessels, extreme dextroposition of the aorta or drainage of the pulmonary veins into the right atrium, there is no actual shunt and there is an adequate pulmonary blood flow, but venous blood is being pumped into the systemic circulation and it is difficult or impossible to direct oxygenated blood to the tissues. Even when the shunt is from the venous to the arterial side, cyanosis develops only if a considerable amount of venous blood is so shunted. This requires either an abnormal communication of large size or a considerably higher pressure on the venous than on the arterial side of the communication.

According to the calculations of Lundsgaard and Van Slyke[127] cyanosis appears in patients with normal hemoglobin if the venous-arterial shunt exceeds 38 per cent of the cardiac output of the heart. In a fifteen year old cyanotic boy with the tetralogy of Fallot (p. 650), Weiss and Löwbeer[212] calculated that the cardiac output was 7.08 liters per minute and that 4.89 liters or 69 per cent of it was shunted from the venous to the arterial side. In a similar case, Segall[184] calculated the shunt to be 73 per cent of the cardiac output. More recent estimations with the aid of intracardiac catheterization[19] have substantiated these extremely high percentages of veno-arterial shunts in cyanotic patients with tetralogy of Fallot. However, in these cases the deficiency in blood supply to the lungs for oxygenation is an equally important factor.[201] This is the basis for the Blalock-Taussig operation, which eliminates cyanosis by increasing the pulmonary blood flow through the creation of an artificial ductus arteriosus. But even with an adequate pulmonary blood flow, cyanosis may appear if the pulmonary blood is not properly oxygenated in the capillaries, e. g., in congenital pulmonary arteriovenous aneurysm.

Polycythemia is not usually a factor in the original development of the cyanosis because the latter appears before the former. However, the subsequent development of polycythemia may intensify the degree of cyanosis both because of the increase in the total amount of hemoglobin (and therefore of the concentration of reduced hemoglobin) and because polycythemia leads to

engorgement of the subpapillary venous plexus (p. 125) and to peripheral circulatory stasis with increased deoxygenation in the capillaries (p. 124).

The cases of congenital heart disease in which cyanosis appears at birth or shortly thereafter have given rise to the terms "blue baby" and morbus caeruleus. Obviously not all cases of congenital heart disease are blue babies or examples of morbus caeruleus. Furthermore, cyanosis at birth may be due to pulmonary atelectasis or intracranial hemorrhage. In some cases of congenital heart disease cyanosis is absent at birth but appears after weeks or months because a compensating open ductus arteriosus becomes obliterated.

The congenital cardiac lesions associated with persistent cyanosis comprise defects of such large size that there is a fairly free mixing of the venous with the arterial blood or there is an associated lesion which raises the normally lower pressure on the venous side of the communication so that it exceeds that on the arterial side. Examples of the first mechanism are the instances of bilocular and trilocular hearts and of persistent truncus arteriosus. Extensive contamination of the oxygenated blood also occurs in cases of complete transposition of the great vessels in which the aorta arises from the right and the pulmonary artery from the left ventricle. Thus the venous blood from the right ventricle is expelled into the aortic or systemic circulation. An example of the second mechanism is seen in cases of pulmonic stenosis with an interventricular septal defect or transposition of the great vessels. The valvular stenosis increases the pressure on the right side of the heart so that it exceeds the pressure in the left ventricle. Therefore blood flows through the abnormal communication from the venous to the arterial side. In cases of uncomplicated pulmonary stenosis, or of uncomplicated ventricular septal defects, cyanosis is usually absent except terminally. Other cases with combined defects leading to a permanent venous-arterial shunt and therefore to persistent cyanosis include: auricular or ventricular septal defects or patent ductus arteriosus associated with right-sided valvular stenosis or atresia; and partial or complete transposition of the arterial trunks with or without septal defects, patency of the ductus arteriosus and valvular lesions. The tetralogy of Fallot (p. 650), in which a ventricular septal defect is associated with pulmonary stenosis and dextraposition of the aorta, is the commonest cardiac anomaly associated with persistent cyanosis in patients reaching the age of puberty. As a rule, persistently cyanotic patients with congenital cardiac lesions other than the tetralogy of Fallot suffer from defects of such seriousness that they die in infancy or early childhood.

Pathogenesis of Clubbing in Congenital Heart Disease

Clubbing of the fingers and toes usually occurs only in those cases of congenital heart disease with persistent and longstanding cyanosis. It was noted in 132 of the 1000 cases analyzed by Abbott while moderate or intense cyanosis occurred in 396 cases of the same series. The soft parts of the fingers and toes, especially of the nailbed, and sometimes of the nose increase in size until they present a drumstick or bulbous appearance. The pathogenesis of clubbing, whether in cases of congenital heart disease or other conditions, is still unclear. In cases of congenital heart disease, clubbing has been attributed to the oxygen unsaturation of the blood with consequent capillary stasis and accumulation of noxious products in the most peripheral parts of the body. On the other hand clubbing has been viewed as a growth phenomenon which suggests an increased

blood flow to the parts affected. The evidence of growth is seen not only in the increased size of the soft parts of the fingers and toes but also in the convex, forward curvature of the nails, this shape resulting from excessive growth within a confined space. The observations of Mendlowitz[138] on maximum heat elimination from the fingers confirm the theoretical expectation that there is an increased blood flow to the affected parts as well as an increase of pressure in the digital arteries.

Direct microscopic study of the capillaries of the nailbed by Redisch and Roesler[164] has revealed a sharp increase in their number, marked dilatation of the venous and of the capillary curve, the presence of many fine, newly formed capillaries and great dilatation of the subpapillary venous plexus. It is likely that these changes in the peripheral venules and capillaries associated with slowing of the circulation as well as the increase in hemoglobin and erythrocyte content of the blood serve to compensate for its oxygen unsaturation. But at the same time an excessive supply of other nutriments may be provided which incidentally promotes the proliferation of the soft tissues and thus produce clubbing.

COMPLICATIONS

Many of the clinical phenomena in cases of congenital heart disease are not due to the lesions themselves but to the complications to which these lesions predispose. These complications are important especially in those subjects who pass adolescence or reach adult life and are apparently asymptomatic or well compensated. The chief complications are: (1) congestive heart failure, (2) subacute (and acute) bacterial endocarditis, (3) pulmonary tuberculosis, (4) paradoxical embolism, (5) cerebral abscess and (6) rupture of the aorta or of a cerebral vessel.

Cardiac failure requires no special discussion here.

Bacterial endocarditis (p. 778).

Pulmonary tuberculosis is more than an occasional complication in cases of congenital heart disease, particularly with pulmonary stenosis. According to Abbott[1] the incidence of tuberculosis is particularly high in the latter disease (9 of 25 cases or 36 per cent) when the ventricular septum is closed. The frequent association of pulmonary tuberculosis with pulmonic stenosis is related supposedly to the deficient blood supply to the lungs and is contrasted with the relative rarity of tuberculosis in the chronically congested lungs of patients with mitral stenosis (p. 583).

Paradoxical embolism (crossed embolism) refers to the passage of a portion of thrombus from systemic veins, usually in the lower extremities or right side of the heart, to the systemic (arterial) circulation. In the normal circulation such an embolus would tend to lodge in the pulmonary artery or its branches, since it could not traverse the pulmonary capillaries which form the only route to the systemic circulation. However, in the presence of a cardiac anomaly permitting direct communication between the arterial and venous circulations, and notably in the presence of an open foramen ovale, a venous thrombus by passing from the right to the left atrium occasionally embolizes a systemic arterial vessel. That this is the mechanism of paradoxical embolism is occasionally demonstrable at necropsy in certain cases in which the thrombus is found straddling both sides of an open foramen ovale.[202]

In the majority of cases a cerebral artery, usually the middle cerebral or one

of its branches, is the site of embolization. But frequently multiple emboli appear, the kidney as well as the brain being commonly affected. Since the origin of paradoxical emboli is usually in the systemic veins, there are often simultaneous uncrossed emboli to the lungs. In all six cases of paradoxical emboli reported by Ingham[103] there were also pulmonary emboli. Usually the pulmonary embolism precedes the paradoxical embolism. In fact, the rise of pressure in the right cardiac chambers consequent to pulmonary embolism is believed to facilitate the venous-to-arterial shunt of thrombotic material through a patent foramen ovale, or through some other auricular or ventricular septal defect. A diagnosis of paradoxical embolism is suggested by occlusion of a systemic artery after pulmonary embolism, provided there is no other obvious cause of the systemic embolization such as bacterial endocarditis, mitral stenosis with auricular thrombi or myocardial infarction with mural ventricular thrombi.

The occurrence of *brain abscess* in cases of congenital heart disease, not due to the direct extension of suppuration from neighboring structures, was pointed out long ago by Ballet.[11] This association has been recently reviewed by several groups of observers.[211, 97, 169] As a rule the abscess develops from a paradoxical embolism in cases with a patent interventricular septum, especially with tetralogy of Fallot, and less often with a defect of the interauricular septum. Bacterial endocarditis is absent in these cases. I have twice seen patients with symptoms of a brain tumor who were discovered to have clinical signs of a ventricular septal defect. Because of this association a diagnosis of cerebral abscess was made and confirmed by surgical exploration. It is presumed, though it is usually difficult to prove, that these cases of brain abscess are examples of paradoxical embolism in which the embolic material contains pyogenic organisms. Because the abscess is a solitary one, it should be amenable to antibiotic and surgical cure if the diagnosis is made. One such cure was recently reported by Smolik and associates.[186]

Spontaneous *rupture of the aorta* in cases of congenital heart disease is usually a complication of coarctation or hypoplasia of the aorta (p. 670).

Cerebral complications and their symptoms have been discussed (p. 637).

THE COMMON TYPES OF CONGENITAL HEART DISEASE

Atrial Septal Defects

Embryology. About the fourth week of fetal life, a membrane, the *septum primum,* grows downward from the superior posterior wall of the atrium and divides it incompletely into right and left chambers. The lower margin of the septum primum has a sickle-shaped defect which is the *ostium primum.* Shortly afterward another opening, the *ostium secundum,* appears in the upper portion of the septum primum. Subsequently a second membrane, the *septum secundum,* whose exact origin is uncertain, develops slightly to the right of the septum primum and fuses with it. It embraces the ostium secundum, leaving an oval opening, the foramen ovale, which functions as a circulatory pathway in the fetus but usually closes shortly after birth. The ostium primum is normally closed during the fifth or sixth week by the downward growth of the septum primum and its fusion with the endocardial cushions which divide the atrioventricular canal into left and right channels. Occasionally, however,

the ostium primum is not closed and persists in adult life as a defect at the lower end of the interauricular septum.

Despite the fusion of the septum secundum and septum primum, the foramen ovale remains patent throughout fetal life and for some time after birth. During fetal life the mixed blood containing the oxygenated blood from the placenta enters the right atrium and is directed by the sinus valve through the foramen ovale into the left atrium. After birth the higher pressure in the left atrium as compared with that in the right causes the valve-like fold about the foramen ovale to occlude the opening. But anatomically, the foramen is still patent in many individuals until the second year of postnatal life. According to Patten,[153] functional closure of the foramen ovale occurs in only 35 per cent of subjects by two weeks of age, but at six weeks 90 per cent and at three months 98 per cent of individuals have a functionally closed foramen ovale. On the other hand, complete anatomic closure of the foramen ovale is found in only 18 per cent of subjects at one year, in 50 per cent at two years. Even among adults, 20 to 25 per cent of hearts at necropsy are found to possess an anatomically open foramen ovale. In most instances it is only a slit-like aperture which just permits a probe to be passed obliquely from the right atrium anteriorly to the left atrium posteriorly (probe-patent foramen ovale).

Pathology and Pathologic Physiology. A patent foramen ovale may be of clinical significance only when it is of sufficient size to permit the passage of blood between the two atria. In the series of 1100 necropsies studied by Thompson and Evans,[202] 6 per cent of the hearts revealed a foramen ovale of more than 7 mm. in diameter while 29 per cent contained merely a probe-patent opening. The flow of blood is from the left to the right atrium. Occasionally the flow is reversed by an increase in right atrial pressure. Paradoxical embolization is a rare complication when this reversal occurs. Defects in the atrial septum may also appear elsewhere than at the foramen ovale. A considerable interatrial septal defect may be due to persistence of the ostium primum in adult life. This appears as a circular or crescentic aperture at the lower end of the atrial septum. It may be associated with a patent foramen ovale. Other portions of the septum may also be the site of small or large openings and multiple defects may be present.

The entire atrial septum may be lacking. In such cases, if the ventricular septum is present, the subject has a cor triloculare biventriculare.[48] This condition is rare, is usually associated with other lesions and offers a very poor prognosis; rarely an individual with this defect lives to the age of thirty with relatively few symptoms. Equally rare and even more serious are the cases in which both the atrial and ventricular septa are completely absent, the heart being termed cor biloculare. There are usually vestiges of the atrial or ventricular septa. It is amazing that cyanosis is often absent through most of the course of the disease, presumably because of a functional if not anatomic segregation of the arterial and venous blood within the single ventricle or atrium. There is a striking tendency for Mongolian idiocy to be associated with defects at the lower end of the atrial septum (persistent ostium primum) which are sometimes combined with a common (undivided) atrioventricular canal.[175]

The majority of cases with a significant atrial septal defect are complicated by a valvular lesion; this association was encountered in more than three quarters of the 61 cases analyzed by Roesler.[172] Usually there is a mitral

stenosis, less commonly an aortic valvular lesion, or both. The clinical syndrome associated with atrial septal defects occurs most often when the septal defect is combined with mitral stenosis. Therefore, this combination of lesions with its attendant clinical manifestations will be described separately. A large uncomplicated interatrial septal defect produces essentially the same physiologic disturbances and clinical picture.[204]

Atrial Septal Defect with Mitral Stenosis

In the French literature, which contains many reports of such cases, the combination of an atrial septal defect with mitral stenosis is known as Lutembacher's[128] disease because of the detailed account given by that author. McGinn and White[134] reported the clinical and pathologic findings in 23 cases culled from the literature and in one case of their own. An extensive analytic review is found in Roesler's[172] report on atrial septal defects, and a more recent one by Bedford, Papp and Parkinson.[13]

Etiology and Pathologic Physiology. Like uncomplicated mitral stenosis, this combination of mitral stenosis with an auricular septal defect occurs predominantly in females. The septal defect is usually large (2 or 3 cm. in diameter) and located near the foramen ovale. It may represent a persistent ostium primum or the functional reopening of a probe-patent foramen ovale by an increase in the left intra-atrial pressure. The mitral stenosis may be a congenital defect since there is almost never a history of rheumatic fever; I have several times examined hearts at necropsy with combined atrial septal defects and mitral stenosis in children below the age of two. However in other cases there may be an acquired rheumatic mitral stenosis.

Due to the obstruction at the mitral orifice, the pressure in the left atrium rises and causes a shunt of blood through the septal defect from the left to the right atrium.[27] As a consequence, the right chambers of the heart and the pulmonary circulation carry an increased quantity of blood, while the left ventricle and aorta distribute a relatively small quantity. A similar effect may be produced by an acquired aortic valvular lesion or hypertension. Cardiac catheterization disclosed a right atrial average pressure of 1.4 mm. Hg, while the pressure in the left atrium averaged 4.1 mm. Hg in the studies of Cournand et al.[42] But the right atrial pressure may be considerably elevated even when the shunt is from left to right.[100] The right ventricular pressure is elevated.[130]

Pathology. The heart is very large and averages 550 to 600 gm. in weight. The enlargement involves particularly the right ventricle and right atrium, which are exceedingly dilated and hypertrophied. Almost the entire anterior aspect of the heart in situ is formed by the dilated right chambers, while the left ventricle appears as a small appendage which is just visible near the apex. Despite the mitral stenosis, the left atrium is usually of normal size or only slightly enlarged because the flow of blood, although obstructed at the mitral orifice, has free egress through the septal defect.

The pulmonary artery, whose diameter is normally less than that of the aorta, is relatively larger in this disease. Occasionally the pulmonary artery and its branches are greatly dilated and may reach aneurysmal proportions. This exaggerated pulmonary dilatation is an essential feature of the disease as described by Lutembacher.[128] The aorta is hypoplastic.

The auricular septal defect and the valvular lesion have been noted.

Clinical Features. There may be no significant symptoms and no interfer-

ence with a normal or even a long life span. When symptoms are present, the most common are exertional dyspnea, palpitation, fatigability or weakness. Often symptoms are precipitated by an upper respiratory infection. Recurrent attacks of pneumonia, pulmonary infarction and pulmonary congestion (left heart failure) are characteristic in some cases. Cyanosis is absent throughout most or all of the course of the disease because the shunt of blood is from the arterial to the venous side of the heart. Late or terminal cyanosis (cyanose tardive) may appear with a reversal of the shunt, if the pressure in the right atrium is made to exceed that in the left because of pulmonary complications or heart failure. Clubbing is absent.

The patients are sometimes underdeveloped, slender or even infantile (habitus gracilis). The skin may be semitranslucent, the bony structure light, puberty delayed and menstruation abnormal. Arachnodactyly may be a significant association.[76] The underdevelopment is attributed to the diminished blood flow through the aorta into the systemic circulation.

Eventually the clinical course is terminated most often by symptoms of right-sided congestive heart failure, with evidences of venous engorgement, subcutaneous edema, ascites and hydrothorax. Subacute bacterial endocarditis is an extremely rare complication.[117a] The occurrence of paradoxical embolism has been mentioned. Furthermore an atrial septal defect represents the only congenital cardiac anomaly which is frequently associated with paroxysmal tachycardia and transient auricular fibrillation. Extrasystoles, auricular flutter, ventricular escape and auriculoventricular dissociation also have been noted.

Hoarseness may result from paralysis of the left recurrent laryngeal nerve due to giant dilatation of the pulmonary artery.[66]

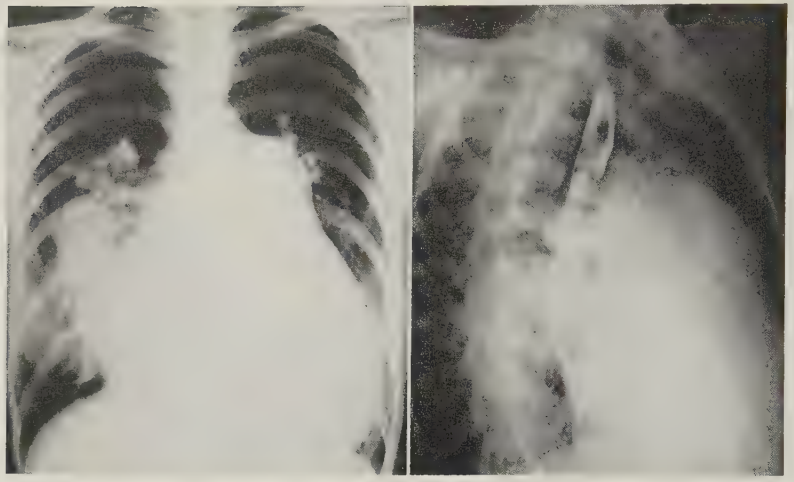
Physical Examination. There may be a left-sided deformity of the chest due to forward pressure of the right ventricle against the precordium. Palpation and percussion reveal enlargement of the heart, the apex being displaced downward and to the left while the right border is extended to the right of the sternum.

A systolic murmur is present in most cases but its location is variable. Most often there is a loud systolic murmur, sometimes accompanied by a thrill in the second or third interspace near the left border of the sternum. But it may also be heard lower near the sternum or at the apex. In about one third of the cases there is an apical diastolic murmur of mitral stenosis. In advanced cases there may be a diastolic murmur of pulmonic insufficiency. The second pulmonic sound often is accentuated.

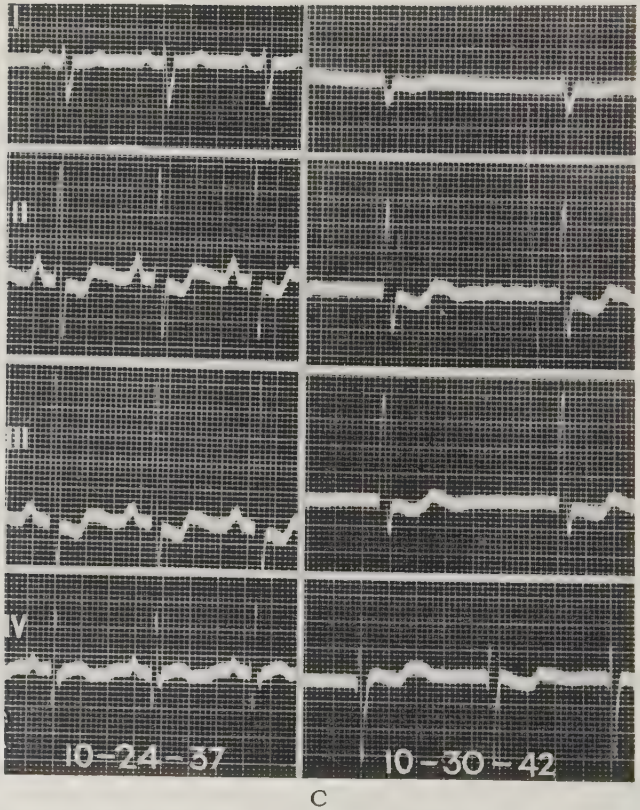
With the development of congestive heart failure, the cervical veins become full. In the presence of auricular fibrillation, which occurs frequently, there may be a systolic pulse in the liver and cervical veins (pp. 620–1); with regular sinus rhythm there is a presystolic venous and hepatic wave (double pulse wave, p. 621) just as in cases of tricuspid stenosis.[55] The radial pulse is often small.

Roentgenology. The essential features are:

1. A prominent pulmonary artery (Fig. 64).
2. A small aortic knob, or absence of the aortic knob.
3. Prominent hilar shadows and large sharply defined branches of the pulmonary artery. These are not invariable findings. The hilar vessels may pulsate (dancing hilum, p. 627). The larger hilar vessels may be mistaken for a mediastinal tumor or lymphoma and needless surgery or radiotherapy under-



A B



C

Fig. 64. Interatrial septal defect. *A*, Posteroanterior view. Huge pulmonary artery and branches.

B, Right oblique view. Rounding and compression of esophagus by large left atrium due to associated mitral stenosis.

C, Electrocardiogram of same case, 10/24/37. Pronounced right ventricular strain. 10/30/42, developed auricular fibrillation. This arrhythmia in congenital heart disease suggests interatrial septal defect.

taken. The left atrium is usually of normal size but may be slightly enlarged. The barium-filled esophagus may be displaced as in uncomplicated acquired mitral stenosis.

4. Sometimes there is a large globular cardiac shadow without striking enlargement of the pulmonary artery or hilar vessels.

These features are diagnostically distinctive. The prominent pulmonary arterial shadows may be observed in some cases of patent ductus arteriosus, while the aortic knob is small in cases with a persistent right aortic arch and in conditions associated with a dilated pulmonary artery. But the generalized cardiac enlargement seen with significant auricular septal defects is unusual with these other conditions. Idiopathic dilatation of the pulmonary artery can usually be distinguished by angiocardiography[85] and by intracardiac catheter studies of oxygen content.

Electrocardiogram. There is usually a right axis deviation and evidence of right ventricular strain. The QRS complexes may be of high voltage, notched and frequently widened.[13] High P waves may be present. The P-R interval is sometimes prolonged. Auricular fibrillation is common toward the end of the disease. Right bundle branch block in a case of congenital heart disease should suggest the presence of an interatrial septal defect.

Cardiac Catheterization (See Diagnosis). The *diagnosis* is based on the finding of a loud systolic murmur in association with pronounced globular enlargement of the cardiac silhouette, especially the right chambers, with small aortic knob and prominent pulmonary artery and branches. Confirmation may be presented by intracardiac catheterization, which reveals a distinctly higher oxygen concentration in the right atrium than in the superior vena cava.[50] Occasionally the catheter slips through the interatrial opening into the left atrium and arterial blood is obtained. The differential diagnosis of this and other congenital lesions is discussed in more detail at the end of the chapter (p. 681).

The *prognosis* is relatively favorable as compared with that in other congenital cardiac lesions. The average age at death is about thirty-five. However the disease may be extremely well tolerated, as in Firket's[69] patient, who lived to be seventy-four and had eleven pregnancies, or in Lutembacher's[128] patient, who survived seven pregnancies and died at the age of sixty-one. Subjects living to seventy-seven and to seventy-six with interatrial septal defects were reported respectively by Tarnover and Woodruff[197] and by Tinney.[204]

Surgical Treatment. An encouraging experimental and clinical report on the closure of cardiac septal defects by through and through sutures of the heart has been made by Murray.[146] In cases of interatrial septal defects, linen, cotton or silk sutures have been used. Heparin was administered, beginning on the second or third day, to prevent embolization.

Ventricular Septal Defects

Defects of the interventricular septum form the second most frequent cardiac anomaly. They were found in 29 per cent of Abbott's[1] 1000 necropsied cases. Some observers believe that this is the most common lesion in cases of congenital heart disease with clinical signs or symptoms. Thus Perry[157] diagnosed a ventricular septal defect in 35 per cent of 119 children with congenital heart disease, and Muir and Brown[144] found the same lesion clinically in 40 of 100 elementary school children with cardiac anomalies.

The cases of uncomplicated ventricular septal defect are known as Roger's disease; Roger[174] described the characteristic murmur associated with this lesion. In three quarters of the cases the ventricular septal defect is associated with other cardiac lesions, especially dextraposition of the aorta and pulmonic stenosis.

Embryology. During the second month of fetal life, the ventricle is divided into two chambers by a septum which grows upward along the anterior and posterior margins. The posterior margin is completed above by joining the posterior endocardial cushion of the atrioventricular canal. The anterior margin is incomplete above, leaving an interventricular foramen. Normally this foramen is closed at about the eighth week by a downward extension of the proximal end of the septum of the bulbus arteriosus. The bulbar septum fuses with the incompleted upper end of the interventricular septum and with the posterior endocardial cushion. The major primary portion of the interventricular septum is a muscular structure. The later segment which closes the interventricular foramen is thin and membranous (septum membranaceum) and is situated in the so-called undefended space of Peacock.

Pathology and Pathologic Physiology. An interventricular septal defect usually results from failure of the bulbar septum to close completely the interventricular foramen. This deficiency of the bulbar septum is associated also with some abnormality in the division of the truncus arteriosus into aorta and pulmonary artery and in the position of these great vessels (see below, p. 650). For this reason, a defect in the ventricular membranous septum is often combined with a dextraposition of the aorta and stenosis of the pulmonary artery. The juxtaposition of the septal leaflet of the tricuspid valve to the fetal interventricular foramen accounts for relatively frequent associated anomalies of that valve. If the disturbances in growth are only slight, the interventricular septal defect may appear as an isolated lesion. Occasionally a communication between the two ventricles is seen in the muscular portion of the ventricular septum. The entire septum may be absent, giving a cor triloculare biatrium if the atrial septum is formed, or a cor biloculare (p. 643) if the atrial septum is also missing. The former is compatible occasionally with the attainment of early adult life. Often there are associated anomalies such as transposition of the great vessels.

The uncomplicated ventricular septal defect may be so small as to permit only the entrance of a probe, or it may be large enough to admit the thumb. It is situated usually in the upper part of the septum, just anterior to the septum membranaceum. Its margins may be thickened due to the tension of the blood stream. Similar sclerosis may appear on the endocardium of the right ventricle opposite the septal defect. Both of these sites may become infected with bacterial vegetations. The heart itself is only slightly enlarged, the enlargement involving chiefly the right ventricle. The pulmonary artery may be somewhat dilated.

The flow of blood through the interventricular opening is from the left to the right ventricle, due to the higher pressure in the former. Hence the systemic blood is not contaminated by unoxygenated blood and there is no cyanosis. With a rise in right ventricular pressure due to pulmonary infections or heart failure, the flow may be reversed with the production of a venous-arterial shunt and cyanosis.

Clinical Features. There are usually *no symptoms* due to the lesion itself. Cyanosis is absent except occasionally during exercise, or as a result of pulmonary infections or heart failure. Sometimes cyanosis is present at birth but disappears later.

The characteristic *physical sign* is a distinctive, prolonged, usually loud and harsh systolic murmur with maximum intensity in the third or fourth left interspace near the sternum. The murmur is very loud at this site in the center of the precordium and becomes progressively fainter as the examiner moves the stethoscope toward the apex or toward the left clavicle. Rarely the murmur is loudest at the left of the xiphoid process. Often it is transmitted to the back where it is heard in the left interscapular or subscapular region. The murmur of an uncomplicated ventricular septal defect is said to be not usually transmitted to the cervical vessels, in contrast with the murmur of the tetralogy of Fallot. But there are occasional exceptions. The murmur may endure through part of diastole and obscure the second sound. In about one third of the reported cases the murmur is accompanied by a systolic thrill which is felt over the site of maximum intensity of the murmur.

Course and Complications. Frequently in asymptomatic subjects a normal life is terminated by some intercurrent disease. Right-sided heart failure with terminal cyanosis is not uncommon in subjects with large defects. In Abbott's[1] autopsied series of cases, 37 per cent died of a complicating bacterial endocarditis. The vegetations are usually situated in the pulmonary conus of the right ventricle where the shunted stream of blood strikes most forcibly. Brain abscess occurs occasionally, more often with uncomplicated ventricular septal defect or tetralogy of Fallot than with any other congenital cardiac anomaly.[169]

Of special interest is the association of *congenital heart block*.[220] In most cases of congenital heart block there is found a defect of the membranous portion of the interventricular septum. Of 44 cases with this conduction disturbance collected by Yater, Lyon and McNabb,[220] 26 had a ventricular septal defect and one had no ventricular septum. The association of congenital heart block with a ventricular septal defect is attributed to the proximity of the bundle of His to the usual site of the defect near the undefended space, so that the same developmental disturbance is likely to cause both lesions. Occasionally an atrial septal defect is also present.[155] Yater et al.[220] believe that congenital heart block is due to a developmental defect of the bundle of His. Congenital heart block in itself is not a serious lesion and does not interfere with life. The serious prognosis in some cases is determined by associated cardiac anomalies. In the series of 44 cases collected by Yater et al.,[220] symptoms were uncommon and cyanosis was absent in 24 and slight or occasional in 14.

Roentgenology. There is no distinctive cardiac silhouette, but there may be slight right ventricular enlargement.

Electrocardiogram. There is no significant change unless there is an associated complete heart block.

Cardiac catheterization discloses a significantly higher oxygen content of the right ventricular blood than of the blood in the right atrium, due to the shunt of arterial blood from the left to the right ventricle.[10]

Surgical Treatment. The promising study of Murray[146] on closure of cardiac septal defects has been mentioned. In cases of ventricular septal defects, through and through cardiac sutures made of fascia lata have been recommended.

The Tetralogy of Fallot

The combination of a ventricular septal defect with pulmonary stenosis, dextraposition of the aorta and right ventricular hypertrophy is known as the tetralogy of Fallot.[68] This syndrome deserves a discussion independent of that on the uncomplicated ventricular septal defect (Roger's disease[174]) because it is one of the commoner forms of congenital heart disease encountered in adult life and because it is one of the congenital cardiac diseases which can be strikingly ameliorated by surgical procedures. It is the commonest clinical form of congenital heart disease in adult life which is associated with cyanosis and clubbed fingers. It occurs much more frequently than isolated pulmonary stenosis or atresia. About three quarters of these latter cases are combined with a ventricular septal defect and transposition or dextraposition of the aorta.

Embryology and Pathogenesis. Cephalad to the primitive ventricle and separated by a fold is another chamber termed the bulbus arteriosus; this in turn is similarly demarcated from the truncus arteriosus. During the fifth to the eighth weeks the proximal portion of the bulbus is absorbed into the right ventricle as the infundibulum or the pulmonary conus arteriosus. The remainder of the bulbus and the truncus arteriosus are divided by a spirally (clockwise) twisted septum to form the pulmonary artery and the aorta. As noted above (p. 648), this septum also grows caudally to help form the membranous part of the interventricular septum and thereby to close the interventricular foramen. The normal growth and twist of the truncus-bulbar septum is such as to cause the pulmonary artery to arise from the right ventricle and the aorta from the left ventricle.[115]

The pathogenesis of the lesions forming the tetralogy of Fallot and similar combinations of malposition of the great vessels has been the subject of controversial theories which have been recently reviewed by Lev and Saphir.[121] These authors applied the studies of Pernkopf and Wirtinger[156] to their own cases and reached the conclusion that the basic abnormality is a disturbance in the absorption of the bulbus as first postulated by Keith.[110] This disturbance is said to be due to an excessive backward torsion of the proximal portion of the bulbus. This mechanism could explain the frequency with which the pulmonic stenosis is situated in the infundibulum (infundibular stenosis), as compared with pulmonary valvular or arterial stenosis.

An ingenious theory supported by many case studies was formulated by Spitzer[189] who attributed the lesions in the tetralogy of Fallot to two essential factors: (1) An inadequate clockwise torsion or even a counterclockwise torsion of the truncus and bulbus arteriosus (see above) and of the septum which divides this vascular tube. (2) Persistence of the reptilian right aorta which should atrophy if development is normal.

Pathology. Since the proper development of the truncus and bulbus arteriosus and their common septum determines the normal position and size of the aorta and pulmonary artery and the completion of the interventricular septum, it is obvious that a disturbance in that development would cause not a single but multiple defects. Hence the frequency of the tetralogy of Fallot as compared with uncomplicated malposition of the great vessels or pulmonary stenosis. Most often the aorta appears displaced to the right so as to arise from both ventricles (reitende or riding aorta); or it may arise from the right ventricle alone (simple transposition or dextraposition of the aorta). Occasionally the

origin of both vessels is transposed, the aorta arising from the right and the pulmonary artery from the left ventricle (crossed or complete transposition of the great vessels). The positions of the aorta and pulmonary artery may appear reversed with respect to each other, but their origin is from the proper ventricle (corrected transposition).

The pulmonic stenosis is often situated below the valve in the region of the infundibulum or conus arteriosus. This may result from encroachment of the partially or completely persistent reptilian right aorta or from improper absorption of the bulbus into the right ventricle. In other cases the stenosis is situated in the region of the pulmonary valve or the artery itself. A bicuspid pulmonic valve is often present and it may add to the stenosis. The trunk of the pulmonary artery may be of lead pencil size or completely occluded (pulmonary atresia). With valvular or subvalvular stenosis, the pulmonary artery is usually hypoplastic but may be dilated (poststenotic dilatation). The poststenotic dilatation may represent an aneurysmal dilatation secondary to the hypoplasia and weakness of the pulmonary wall.

If the pulmonary stenosis is severe or the pulmonary artery or valve is completely occluded (pulmonary atresia), the ductus arteriosus must be patent to permit life. Death usually supervenes after a few months as the ductus becomes obliterated. Rarely a blood supply to the lungs is maintained by the development of a remarkable collateral circulation arising from the aorta or its branches,[58] as in cases of persistent truncus arteriosus with bronchial arteries supplying the lungs. The collaterals consist of dilated bronchial, esophageal, thyroid, mediastinal or other vessels.

Occasionally, instead of a pulmonary stenosis or atresia, the infundibulum and pulmonary artery are dilated or of normal size and associated with dextraposition of the aorta, ventricular septal defect and right ventricular hypertrophy. This is known as the tetralogy of Eisenmenger.[63, 180, 81, 19]

The ventricular septal defect, the third element in the tetralogy of Fallot, is usually at the upper portion of the interventricular septum, anterior to the undefended space. Occasionally the entire septum is lacking.

The right ventricle is considerably hypertrophied. When the site of the pulmonary stenosis is in the infundibulum, a third (accessory) ventricular chamber may be formed in the right ventricle just above the stenosis.

A tendency to the development of widespread pulmonary thrombosis due to the polycythemia and to diminished pulmonary blood flow has been reported by Rich.[167]

Pathologic Physiology. As a result of the pulmonary stenosis and the increased venous return to the right heart, the right ventricular pressure is elevated and venous blood is shunted through the interventricular septal defect into the overriding aorta. The aorta also receives oxygenated blood from the left ventricle and the total systemic blood flow exceeds that through the narrowed pulmonary artery. The subnormal pulmonary blood flow[19] and consequent deficiency in arterial oxygenation are fundamental elements in the circulatory disturbance. (See p. 639 for cardiac output and size of shunt.)

Arterial oxygen unsaturation results in polycythemia and in dilatation of the peripheral capillary bed, both of which partially compensate for the anoxemia, especially at rest. However, during exercise, continuous recordings with the Millikan oximeter have disclosed a striking fall in oxygen saturation[142] which accounts both for the increase in cyanosis and the development of

dyspnea. In normal persons there is no reduction in oxygen saturation during exercise. Furthermore, patients with tetralogy of Fallot experience a fall in the oxygen consumption per liter of ventilation during exercise, while normal individuals consume more oxygen per liter of ventilation under the same conditions. Patients with the tetralogy of Eisenmenger, whose pulmonary circulation is close to normal, experience a fall in oxygen saturation during exercise, but their $\frac{\text{oxygen consumption}}{\text{ventilation}}$ ratio rises in normal fashion.[19] When normal patients breathe 100 per cent oxygen, the arterial oxygen saturation rises from about 97 per cent to 100 per cent within three minutes. Patients with tetralogy of Fallot require ten to fifteen minutes under the same circumstances to reach maximum oxygen saturation (which is still below normal).[96]

Clinical Features. The tetralogy of Fallot is the one form of congenital heart disease which accounts for the great majority of cases of persistent cyanosis and clubbing in adolescence and adult life. Ninety per cent of the so-called cases of morbus caeruleus in adults are due to the tetralogy of Fallot. *Cyanosis* is present from infancy. It may be absent in the first few months of life while the ductus arteriosus is still patent and serves as an accessory route for blood (from the aorta) to reach the pulmonary circulation. *Clubbed fingers* usually appear months or years after the appearance of cyanosis. Eventually clubbing may be marked while the cyanosis is only slight. The cyanosis may become intensified during exercise, pulmonary infections and late in the course of the disease when right-sided heart failure develops. *Cyanosis retinae* is usually present and occurs early. *Suffusion of the eyeballs* is often associated with secondary *polycythemia.*

The pathogenesis of cyanosis and clubbing in congenital heart disease was discussed above.

Dyspnea on exertion is a common complaint. (Its pathogenesis has been discussed, p. 106.) Paroxysmal attacks of dyspnea may occur, generally after exercise, and accompanied by an intensification of cyanosis. Orthopnea is absent; in fact the dyspnea may be intensified when the patient is erect (orthostatic dyspnea). Fatigability and weakness are frequent symptoms. Characteristically the child with tetralogy of Fallot assumes the squatting or knee-chest position when dyspneic or tired from exertion.

Polycythemia, often of intense degree, is usually present. The blood volume is increased, primarily due to an increase in red cell volume.[147] The hematocrit is very high. Quite frequently, and especially in the late stages of the disease, patients suffer from dizziness, syncopal attacks, epileptiform convulsions and transient or permanent paralyses. Death may occur during a syncopal attack. These cerebral symptoms are secondary to anoxia of the brain, and are probably related to the vascular disturbances associated with polycythemia. Cerebral thrombosis, encephalomalacia and cerebral hemorrhage may occur. Epistaxis, hemoptysis and hematemesis have also been reported as resulting from the polycythemia. Brain abscess is more often associated with this than with any other congenital cardiac lesion.[169] Orthostatic albuminuria due to disturbance of the renal circulation has been noted. The patients with tetralogy of Fallot may be of normal intelligence or they may be mentally and physically retarded.

Cardiac Signs. Usually there is a *systolic murmur* to the left of the sternum in the second or third interspace, occasionally in the fourth. It has been claimed that the lower location corresponds to an infundibular stenosis, the higher to

a pulmonary valvular or arterial stenosis. The murmur may or may not radiate to the cervical vessels. Occasionally there is no murmur.

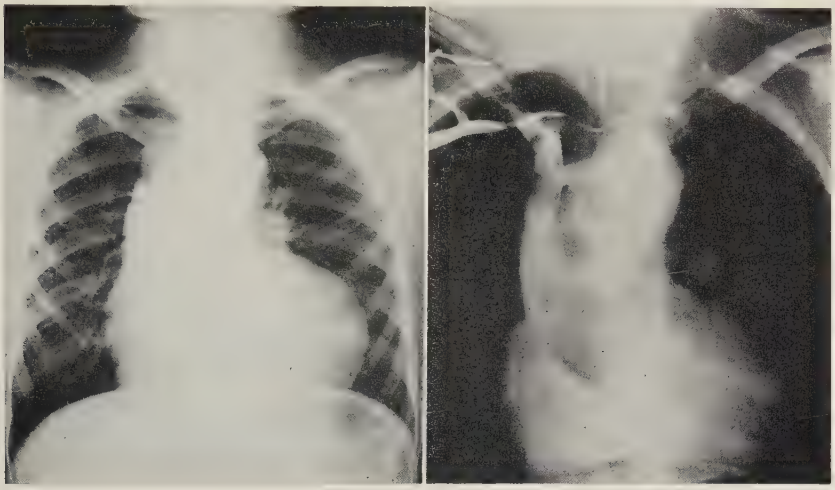
A systolic *thrill* is often present but less frequently than in uncomplicated cases of pulmonic stenosis or ventricular septal defects.

The *second pulmonic sound* is weak or absent, but occasionally it is normal.

Precordial bulging, systolic pulsation in the second and third interspaces and epigastric pulsation may result from the hypertrophy of the right ventricle.

Roentgenology. The roentgenologic findings have been described by Raab[162] and by Papp.[152] The following are the usual features after the first few years of life when the heart may appear normal.

1. The left lower contour is plump and prominent, and the apex is elevated and blunted, resembling a sheep's nose. The blunting of the left contour, often



A B

Fig. 65. *A*, Tetralogy of Fallot. Coeur en sabot configuration.
B, Angiocardiogram of same case. Simultaneous opacification of aorta and pulmonary artery.

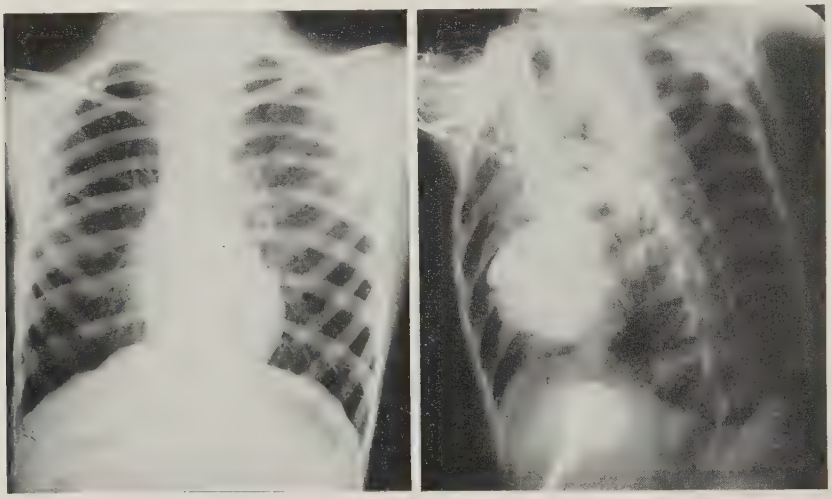
associated with a transverse rectangular enlargement, gives rise to the description of *coeur en sabot* (like a wooden shoe) (Fig. 65). This differs from the aortic configuration (p. 595) in which the left lower contour is elliptical and not cut off, and in which oblique views disclose enlargement of the left ventricle, not of the right. In general, the cardiac enlargement in tetralogy of Fallot is not pronounced, and the coeur en sabot configuration is often absent in children (Fig. 66).

2. The waist of the heart forms a concave depression, i.e., the left middle contour formed by the pulmonary conus and artery is small or absent. In the left anterior oblique view the pulmonary window is abnormally clear. There is no pulmonary congestion. The hilar pulmonary vessels are small and their pulsations are not visible. These findings contrast with the prominent pulmonary conus and arterial shadow in Eisenmenger's tetralogy and in Lutembacher's syndrome.

3. The shadow of the great vessels may be narrow in the anterior-posterior view, but the aortic shadow becomes wider and prominent in the left-anterior-oblique view.

4. In about 20 per cent of cases there is a right aortic arch (p. 671), visible as a prominence of the aortic knob to the right of the sternum within the shadow of the superior vena cava.

Angiocardiography. There is a prompt passage of the diodrast from the right ventricle simultaneously into the aorta and pulmonary artery. The aorta and all its branches are visualized within 3 seconds after injection instead of in 5 or 6 seconds as is normal. Relatively little of the contrast media enters the pulmonary artery and discloses the stenosis of this vessel as contrasted with the normal or large pulmonary artery seen in Eisenmenger's tetralogy.[53a] Angiography is also of value in disclosing the position of the aortic arch and in differentiating other congenital anomalies which might otherwise be mistaken for the tetralogy of Fallot and improperly submitted to surgery.



A B

Fig. 66. Tetralogy of Fallot. *A*, Posteroanterior view. Note coeur en sabot configuration is not present.

B, Angiocardiogram of same case. Left oblique view. Simultaneous opacification of aorta and pulmonary artery.

The Electrocardiogram. There is usually a pronounced right axis deviation and there may be an RT depression and an inverted T_3 indicative of right ventricular hypertrophy. The latter may be well demonstrated by serial precordial leads showing low R waves and deep S waves over most of the chest wall until the left axilla is reached. The P waves are often of high voltage.

The Circulation Time. The injection of 3 minims of ether diluted with 10 minims of saline produces paresthesias of the lips and extremities due to the drug's entrance into the systemic circulation.[15] Arm-to-tongue (saccharin) time may be abbreviated almost to the ether time, since the saccharin passes directly into the systemic circulation by way of the shunt, without traversing the pulmonary circulation as it usually does.

Cardiac Catheterization. The right ventricular pressure is elevated. The *pulmonary arterial pressure is lower than that in the right ventricle,* denoting pulmonary stenosis. Eisenmenger's complex differs in that there is an elevation in both the pulmonic systolic and diastolic pressures and the pulmonic pressure is essentially equal to that in the right ventricle. Occasionally the catheter

may pass through the ventricular septal defect from the right ventricle into the aorta.

The *oxygen concentration* in the right ventricle exceeds that in the right atrium as in other cases of ventricular septal defects.

In many cases of tetralogy of Fallot the flow in the pulmonary capillaries exceeds that in the pulmonary artery, indicating a significant collateral circulation to the lungs,[19] but the effective pulmonary blood is still diminished. The pulmonary blood flow in Eisenmenger's complex is normal or slightly reduced.

Differential Diagnosis. The diagnosis of congenital cardiac lesions in general is discussed later (p. 681). Here we are concerned with the differentiation of those congenital lesions associated with cyanosis which may be confused with the tetralogy of Fallot, but which cannot be corrected surgically. Mention will be made also of other congenital lesions which, like the tetralogy of Fallot, can be ameliorated by the creation of an artificial ductus arteriosus.

Conditions Amenable to Surgical Improvement (Blalock-Taussig Operation):

Tricuspid atresia with defective development of the right ventricle. There is a right-to-left shunt through a patent foramen ovale. Some left ventricular blood reaches the right ventricle through a ventricular septal defect. There is a small pulmonary blood flow from the diminutive right ventricle. The clinical picture and even the roentgenogram may resemble that of tetralogy of Fallot. The diagnosis is made by the association of cyanosis and a cardiac murmur with left axis deviation in the electrocardiogram.

Cases of nonfunctioning right ventricle, defective development of the right ventricle and single ventricle with pulmonary atresia are similar to the above in the occurrence of cyanosis due to a large venoarterial shunt and subnormal pulmonary blood flow.

Truncus arteriosus is amenable to surgical correction when the pulmonary oxygenation occurs by way of the bronchial arteries arising from the truncus, provided there is a rudimentary pulmonary artery which can be anastomosed with a systemic artery. The diagnostic feature is the sharp shelf-like angulation of the right ventricle in the left anterior oblique view, on roentgenologic examination. Cyanosis, a loud systolic murmur and thrill, and absence of the fullness of the x-ray contour of the pulmonary conus are similar to the findings in tetralogy of Fallot.

Pulmonary atresia with or without dextraposition of the aorta, with or without defective development of the right ventricle, is also an indication for operation. Very early cyanosis and clubbing, intense dyspnea, right ventricular enlargement and narrow shadow of the great vessels are the distinctive features.

Differentiation of Cardiac Anomalies Not Amenable to Operation. Eisenmenger's tetralogy consists of ventricular septal defect, overriding aorta and right ventricular hypertrophy, but the pulmonary artery is not narrowed and may be dilated and the pulmonary valve is normal.[180, 81] The pulmonary blood flow is normal or almost normal.[19] The Blalock-Taussig operation, designed to enhance an inadequate pulmonary blood flow, is therefore not indicated.

Cyanosis starts much later and is usually less intense than in cases of Fallot's tetralogy; the polycythemia is slight or absent. The second sound is usually distinct or loud. Hoarseness may occur as a result of pressure of the dilated pulmonary artery on the left recurrent nerve.

Roentgenologic examination reveals a normal pulmonary salient and there

may be distinct hilar pulsations in contrast with the findings in tetralogy of Fallot. Angiocardiography, by disclosing the normal size of the pulmonary artery, provides a more definite differentiation from tetralogy of Fallot at the same time that it discloses the dextraposition of the aorta. Blood oxygen and pressure studies with the aid of cardiac catheterization reveal a relatively normal pulmonary blood flow, compared to the pronounced diminution in tetralogy of Fallot. The systolic and often the diastolic pressure in the pulmonary artery are elevated in cases of Eisenmenger complex but not in cases of Fallot's tetralogy.

Complete transposition of the great vessels. This is distinguished by the more intense cyanosis and dyspnea starting at birth or in the first weeks of life. Cardiac enlargement occurs early in contrast with the findings in the tetralogy of Fallot. Angiocardiography may reveal the transposed origins of the great vessels. In cases with a patent ductus arteriosus and foramen ovale the head, trunk and upper extremities are more cyanotic than the lower extremities. Although the Blalock operation is not indicated, a pulmonary vein - superior vena caval anastomosis has been recommended (see p. 679).

Course and Complications of Tetralogy of Fallot. Most patients with the tetralogy of Fallot die in the first two decades of life as a result of congestive heart failure, cerebral lesions complicating polycythemia, bacterial endocarditis or pulmonary infections including tuberculosis. Occasionally, however, patients reach adult life and are capable of normal activity with few symptoms. The greatest longevity was reported in the case of a famous American musician who died of a stroke at the age of fifty-nine.[213] Middleton and Ritchie[141] recently reported another case of tetralogy of Fallot in which death from congestive heart failure occurred at forty-five.

Surgical Treatment. The purpose of surgical procedures for tetralogy of Fallot is to increase pulmonary blood flow and oxygenation of blood by anastomosing a systemic artery to a pulmonary artery.

In the procedure devised by Blalock and Taussig[22] a subclavian or innominate artery is anastomosed end-to-side (occasionally end-to-end) to the right or left pulmonary artery, near its origin. In the procedure of Potts, Smith and Gibson,[160] a direct side-to-side anastomosis is made between the aorta and pulmonary artery, with the aid of a clamp which does not completely interrupt the circulation in these vessels during the anastomosis. Blalock usually makes his incision in the third right interspace but when preoperative examination reveals a right aortic arch, the incision is on the left side. In the Potts-Smith procedure the incision is on the same side as the aortic arch.

Ideally, patients should be operated upon between the ages of three and twelve. The severity of anoxemia, incapacity, dyspnea, and degree of reduction in pulmonary blood flow, response to exercise and failure to gain weight are factors determining the urgency of the operative procedure.

The results of successful operation are often dramatic and the clinical improvement striking. The pulmonary blood flow and oxygen saturation are increased. Cyanosis disappears and exercise tolerance is greatly improved so that previously incapacitated children can run and play. However, there is some enlargement of the heart postoperatively and it is probable that these operated patients will subsequently succumb to congestive heart failure as do patients with congenital patent ductus arteriosus or other arteriovenous shunts.

The mortality rate in the first 350 operations performed by Blalock varied

from 11 to 25 per cent according to the age group, with an overall mortality of 15.7 per cent. Operative complications included cerebral thrombosis, hemorrhagic pleural effusions, pulmonary edema, pneumothorax and local thrombosis at the anastomotic site. In some cases the operation could not be completed because the pulmonary pressure was too high, there was a single pulmonary artery, the pulmonary arteries were too small or the systemic artery was too short to permit anastomosis. In a smaller series of 40 cases operated upon by Murray,[145] the mortality rate was 7.5 per cent, and in a series of 45 operated cases reported by Potts and Gibson,[159] the mortality rate was 8.8 per cent.

Patent Ductus Arteriosus

In recent years more attention has been devoted to the recognition and differential diagnosis of patent ductus arteriosus (Botalli) than to almost any other congenital cardiac anomaly. For it is now possible by surgical means to close this abnormal communication and thus ameliorate or prevent the development of cardiac failure and other serious complications of the lesion. This is of special importance because of the high incidence of patency of the ductus among clinically significant cardiac anomalies. According to Abbott's[1] figures for autopsied cases, a patent ductus arteriosus occurred 150 times among 1000 cases of congenital heart disease, of which 92 were uncomplicated; it was exceeded in frequency only by auricular and ventricular septal defects. But in clinical experience, symptoms or signs of congenital heart disease after the first few years of life are due to a patent ductus as often as to any other congenital cardiac lesion. Patent ductus arteriosus occurs about three times as frequently among females as among males.[112, 122]

Embryology and Pathogenesis. The ductus arteriosus arises from the sixth left aortic arch and connects the main or left pulmonary artery with the descending arch of the aorta just below the origin of the left subclavian artery, at the termination of the so-called isthmus of the aortic arch. In fetal life, the blood from the right atrium which comes from the superior vena cava, and which does not pass through the foramen ovale, is expelled into the right ventricle and the pulmonary artery. Almost all the blood from the pulmonary artery passes through the wide patent ductus arteriosus to the descending aorta and its branches to supply the lower half of the body. Only a minute portion of the pulmonary arterial blood reaches the nonfunctioning lungs.

According to Patten,[153] however, the blood supply to the lungs increases gradually in fetal life until shortly before birth a fair pulmonary circulation develops. But it is only after birth, when the lungs assume their respiratory function and their alveoli and the pulmonary vessels expand, that the major quantity of blood from the main pulmonary artery traverses the pulmonary circulation, while less and less is shunted through the ductus arteriosus. It is uncertain whether the ductus ceases to function immediately after birth[12] or gradually after an interval of weeks.[181] Anatomic closure usually occurs by the end of the third month (in about 80 per cent of cases) and at the end of one year the ductus is obliterated in 95 per cent of cases. When the ductus closes, it is converted into a fibrous cord known as the ligamentum arteriosum.

Many theories have been offered to explain the mechanism of closure of the ductus arteriosus. The mechanical theory, as indicated by Klotz,[114] maintains that the ductus closes because of a fall in its blood pressure as the pulmonary arterial stream is deviated to the functioning lungs. According to Klotz,[114]

when the blood pressure has fallen, the extremely muscular walls obliterate the lumen by their tonic contraction and initiate the process of fibrosis. On the other hand, persistent patency of the ductus arteriosus results from the maintenance of a relatively high pressure in this canal. According to the studies of Kennedy and Clark[111] the oxygen in the blood is the important factor in closure of the ductus arteriosus.

Pathology. From the standpoint of surgical management it is important to recognize two groups, namely, patent ductus arteriosus with associated cardiac anomalies, and uncomplicated patent ductus. Among the associated lesions are infantile coarctation of the aorta, complete transposition of the great vessels, pulmonary atresia or severe pulmonary stenosis. In most of these cases patency of the ductus is essential to the maintenance of life.

The patent ductus arteriosus usually forms a cylindrical tube of variable caliber and most often less than 1 cm. long in the adult. Or the communication may be of the window type in which there is merely a fistula between the aorta and pulmonary artery. In such cases surgical ligation or section may be impossible. The ductus is sometimes funnel-shaped and wider at the aortic end; it may be aneurysmal and its lumen filled with thrombus. Rarely the pulmonic end is incompletely closed by a membrane.

The pulmonary artery and its branches become widened. Rarely there may be an aneurysmal dilatation of the pulmonary artery. Both ventricles are somewhat dilated and hypertrophied.

Pathologic Physiology. In uncomplicated patency of the ductus arteriosus, the higher pressure in the aorta shunts blood from that vessel into the pulmonary artery during both systole and diastole. Since the pulmonary artery receives blood from the aorta as well as from the right ventricle, the pulmonary blood flow is above normal; the vessel becomes dilated and its pulsations may be exaggerated.

According to the measurements of Burwell, Eppinger and Gross[35] the shunt was of great magnitude, from 4 to 19 liters of blood flowing per minute from the high pressure area in the aorta to the low pressure area in the pulmonary artery. The aortic-pulmonary shunt also results in increased work for the left ventricle. According to Wilken[214] the cardiac output is almost doubled and according to Eppinger, Burwell and Gross[65] it is two to four times normal. Eppinger and his associates[65] calculated that 45 to 75 per cent of the blood pumped by the left ventricle into the aorta is shunted through the ductus and lungs back to the left side of the heart without supplying the periphery of the body. However, the shunt is probably much less in many asymptomatic cases.

Dilatation and hypertrophy of the left ventricle are usually present, although in most asymptomatic cases this is not demonstrable clinically. On the other hand Eppinger and Burwell[64] observed a moderate degree of left ventricular enlargement roentgenographically in 8 of 9 patients who were operated upon for a patent ductus. The presence and extent of left ventricular enlargement depend on the degree of left ventricular strain. The leakage of blood from the aorta to the pulmonary artery is accompanied by a fall in diastolic pressure similar to that in cases of aortic regurgitation.

In infants there may be a reversal of flow with a venous-arterial shunt during crying, sucking or coughing. Such a reversal with transient or terminal cyanosis may occur also during pulmonary infections and heart failure or in the cases combined with other cardiac anomalies.

The following clinical discussion applies to the cases of uncomplicated patency of the ductus arteriosus.

Clinical Features. In many if not most cases there are no symptoms due to the lesion. Cyanosis is absent, although it may occur rarely with pulmonary vascular disease and pulmonary hypertension.[54] When symptoms appear, they are most often exertional dyspnea and palpitation. The dyspnea is probably due to the increased pulmonary blood flow and consequent pulmonary congestion. Occasionally the subjects with a patent ductus are slender, undersized and underdeveloped[158] (habitus gracilis) and pale. The underdevelopment is attributed to a diminished systemic arterial blood supply as denoted anatomically by hypoplasia of the aorta. This results from the short circuit of a large portion of the aortic blood through the pulmonary circuit (supra).

The *physical signs* are characteristic. The pathognomonic sign is the *Gibson murmur*[77] which is variously described as continuous, machinery-like, train-in-tunnel, humming-top, churning, sawing, etc. It is a long and rumbling murmur which occupies most of systole and diastole (Fig. 67*D*). There is often an accentuation in late systole. The murmur may be diffuse but usually is localized or loudest in the second left interspace near the sternum, the site of the dilated pulmonary artery. Occasionally it is best heard in the third left interspace near the sternum. The systolic element radiates to the cervical vessels and often posteriorly. A *systolic thrill* is usually and a diastolic or continuous thrill is rarely palpable over the site of maximal intensity of the murmur. Muir and Brown[144] heard the above-mentioned continuous murmur in 60 per cent of their 20 cases.

Absence of the machinery-like continuous murmur may be due to variations in the size and conformation of the open ductus and the degree of dilatation of the pulmonary artery.[112, 122] As a rule, if there is no continuous murmur, there is a rough, long *systolic murmur* with maximum intensity in the second left interspace, near the sternum, or occasionally in the first or third left interspace. In infants and young children there may be no murmur at all or a systolic murmur only, until the shunt becomes of significant size and the pulmonary artery dilates. Occasionally a diastolic murmur is heard to the left of the sternum without any concomitant systolic murmur.

The *second pulmonic sound* is accentuated and may be reduplicated. It is of value in differentiating a patent ductus arteriosus from pulmonic stenosis, since the second pulmonic sound is weak or absent in the latter condition.

Percussion may reveal a thin, rectangular area of dullness in the second and third left interspace (Gerhardt's dullness) overlying the dilated pulmonary artery. This is inconstant or difficult to demonstrate by physical examination.

When the ductus arteriosus is widely patent and there is a considerable arteriovenous shunt, one often encounters the peripheral circulatory phenomena seen in cases of free aortic regurgitation (p. 597). These result from the aortic regurgitation of blood into the pulmonary artery during diastole. There is a *high pulse pressure*, which may be due in part to an elevation of the systolic pressure but chiefly to a sharp drop in the diastolic pressure. The diastolic pressure may fall sharply during exercise. In addition to the high pulse pressure there may be a *Corrigan pulse, capillary pulsation, Duroziez's sign* (pistol-shot femorals) and other circulatory phenomena often associated with aortic insufficiency. *Microplethysmography* usually discloses characteristic changes in the pulse wave of the finger, including blunting of the apex of the wave, loss of

differentiation between "systolic" rise and "diastolic" fall and loss of dicrotic notch.[137] Occasionally the blood pressure is higher in the right arm than in the left and the *radial pulses are unequal,* but this probably represents an associated coarctation of the aorta with stenosis of the orifice of the left subclavian artery. An infrequent sign is the *pulsus paradoxus.*

Roentgenology. (1) The size of the cardiac silhouette is usually normal when the shunt is small. With large shunts there is an enlargement of the left ventricle and to a lesser extent of the right ventricle.

(2) The characteristic feature, although not invariably present, is a prominence of the pulmonary arc in the left upper portion of the cardiac silhouette[53]

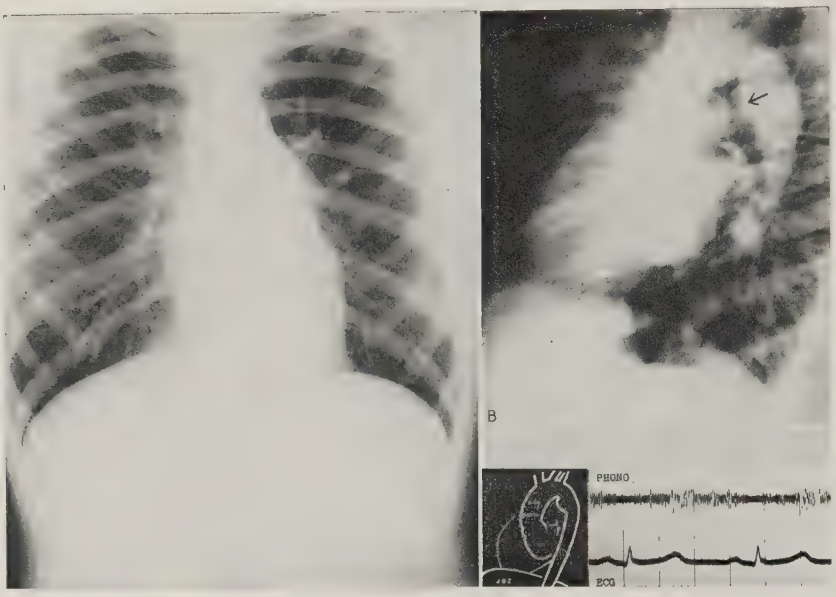


Fig. 67. Patent ductus arteriosus. *A,* Conventional posteroanterior view. Prominent pulmonary artery segment.

B, Angiocardiogram. Left oblique view. Fusiform dilatation just beyond aortic isthmus where ductus is attached (arrow).

C, Diagram of angiocardiogram.

D, Machinery type continuous systolic-diastolic murmur.

(Fig. 67*A*). This is known as the x-ray cap of Zinn. The bulging cap of Zinn represents the dilated pulmonary artery. In other cases with extremely loud murmurs, the shunt is often smaller, the pulmonary artery only slightly dilated and the pulmonary arc less conspicuous roentgenoscopically.

(3) Not only is the pulmonary arc prominent in most cases but its pulsation is considerably exaggerated. The hilar shadows are also prominent both in size and pulsation. These pulsations are rarely as striking and much less frequent than in cases of auricular septal defect (Lutembacher's syndrome[128]).

(4) Pulmonary congestion may be present if the shunt is of considerable size.

The enlargement of the pulmonary artery and conus may be observed most readily in the right oblique view. In the left anterior oblique view, a large

ductus arteriosus may partially obscure the window of the aorta. A valuable diagnostic sign, occasionally present, is a calcified plaque near the caudal end of the arch of the aorta (i.e., the site of junction of the ductus and aorta) in young persons, in whom arteriosclerotic calcification of the aorta is otherwise rare.

Angiocardiography usually reveals a localized dilatation of the descending aorta just beyond the isthmus[191] (Fig. 67*B* and *C*). This characteristic bulge or dilatation may be due to the infundibulum of the ductus or a traction aneurysm of the aorta caused by the ductus. Sometimes patency of the ductus is indicated by prolonged or renewed visualization of the pulmonary artery after there is no longer any contrast medium in the right ventricle.

Electrocardiogram. The electrocardiogram is usually normal. There is generally no axis deviation. These negative findings are important in differential diagnosis.

Cardiac Catheterization. The blood oxygen content is significantly higher in the pulmonary artery than in the right ventricle.[51] The pulmonary arterial pressure and that in the right ventricle may be elevated.[100, 51] The pulmonary capillary flow exceeds that in the pulmonary artery, since the pulmonary capillaries also receive blood through the aortic-pulmonary shunt.

Diagnosis and Differential Diagnosis. The diagnosis of patent ductus arteriosus is based essentially on the presence of the typical machinery-like murmur. Confirmation is supplied by roentgenologic findings of a prominent pulmonary conus and artery, by angiocardiographic demonstration of an aortic bulge at the site of the ductus, and by cardiac catheterization which reveals a higher oxygen concentration in the blood of the pulmonary artery than in that of the right ventricle. The absence of distinct right or left axis deviation is also helpful in distinguishing uncomplicated patent ductus from other cardiac anomalies. The diagnosis is usually relatively simple and definite. Keys and Shapiro[112] encountered only two diagnostic errors in 134 patients who were operated upon for patent ductus. Obviously there were other instances in which operation was not performed because of doubt as to the diagnosis. Occasionally, in young children, there is only a harsh systolic murmur. In such cases, the diagnosis of patent ductus arteriosus must be confirmed by the presence of a high pulse pressure and by angiocardiographic and catheterization findings as noted above.

A *venous hum* gives a continuous murmur, which however is loudest in diastole, is heard also to the right of the sternum and changes in intensity with changes in position of the head and neck.

Aortic septal defect (in a truncus arteriosus) may be associated with a continuous murmur which, however, has its maximal intensity over the lower end of the sternum. The heart is usually much larger than in cases of a patent ductus. A similar murmur occurs in rupture of a congenital aneurysm of the sinus of Valsalva into the pulmonary artery or right chambers, but there is a history of sudden onset of the murmur in adult life.

Atrial septal defect may be mistaken for patent ductus arteriosus when the latter is diagnosed in the absence of the characteristic continuous murmur. Their differentiation has been discussed by Nichol and Brannan.[148] The electrocardiogram usually shows pronounced right ventricular strain in atrial septal defects, but no axis deviation in patent ductus. Angiocardiography and intracardiac catheterization will differentiate the two conditions. Occasionally patent ductus will be found to coexist with an atrial septal defect.

Course and Complications. Many patients never have symptoms referable to the patent ductus and die of independent causes. Unfortunately the available statistics which are based on autopsied cases, usually reported because of some special complication, are misleading in so far as they are not likely to include the more favorable asymptomatic cases.[16] According to Abbott[1] the average age at death is twenty-four years, and according to Keys and Shapiro,[112] thirty-seven years, but some patients have a normal life span. White described a case of patency of the ductus arteriosus in which death occurred at the age of sixty-six.[212a]

The commonest complications and causes of death are *congestive heart failure* and *bacterial arteritis or endocarditis.* According to Abbott,[1] 43 per cent of 92 fatal cases of patent ductus arteriosus died of sudden or slow cardiac failure. In our experience the patent ductus arteriosus is the congenital lesion most often complicated by bacterial endocarditis or endarteritis.[125] According to Abbott,[1] this complication occurred in 37 per cent of cases above the age of two and 30 per cent of all cases including infants. In the series of 60 cases reported by Keys and Shapiro[112] bacterial endocarditis was the cause of death in 42 per cent. This figure is probably higher than the actual incidence, due to the greater tendency to report such cases than those without this interesting complication. The vegetations usually appear in the pulmonary artery at the opening of the ductus where they may be localized or they may extend down the artery for a short distance or they may almost occlude it. Sometimes the pulmonary valves are involved. A bacterial endocarditis of the aortic valves is not infrequently associated with the bacterial pulmonary arteritis. An interesting feature of bacterial arteritis in cases with patency of the ductus is the occurrence of embolic infarction of the lung with hemoptysis and fever, the clinical picture simulating pulmonary tuberculosis.[157] Pulmonary abscess or suppurative bronchopneumonia may result from the emboli.

Other complications are less common. Occasionally the dilated or even aneurysmal pulmonary artery or ductus arteriosus ruptures, causing thoracic hemorrhage and death. A dissecting aneurysm of the pulmonary artery may develop. Thrombosis of the ductus arteriosus occasionally leads to pulmonary embolism. Paradoxical embolism rarely results from the passage of thrombotic material from the left atrium by way of the aorta and patent ductus to the lung. Occasionally there is hoarseness or aphonia due to paralysis of the left recurrent laryngeal nerve probably caused by the pressure of the dilated ductus arteriosus or pulmonary artery.[38]

Treatment. Surgical closure of the patent ductus corrects the abnormalities in circulatory dynamics, restores normal cardiac size, and eliminates the clinical symptoms and the risk of heart failure, bacterial endocarditis or other complications of a patent ductus. Following operation the patient's hands and feet become warmer and the capacity for ordinary activity or physical exertion is increased. Patients with exertional dyspnea, palpitation, fatigability, weakness and chest pain are completely or almost completely relieved of these symptoms. Children who were malnourished and underdeveloped gain weight and improve in growth. The murmur and thrill disappear. The diastolic pressure rises and the pulse pressure falls. The heart rate is slowed, as after the obliteration of other arteriovenous aneurysms (p. 600). The work of the heart as well as its size is diminished. The first successful operation was reported by Gross and Hubbard,[93] and series of operated cases were subsequently described by Gross,[90] by Bullock, Jones and Dolley[34] and by Gilchrist.[78]

The technic of the operation has been described by Gross[90] and by Jones, Dolley and Bullock.[106] At first the ductus was closed by multiple ligatures, but recanalization occurred in about 10 per cent of cases. To avoid this, Gross resorted to cutting the ductus and suturing the cut ends. Occasionally section of the ductus or even passing of ligatures cannot be performed because the ductus is too short. In reports of 343 patients operated upon by various surgeons for an uninfected patent ductus, the mortality rate was just below 5 per cent while Gross[90] reported only 4 deaths in 180 consecutive cases. The mortality rate for closure of a patent ductus with bacterial endarteritis in 88 cases was 28.4 per cent. Not uncommonly the recurrent laryngeal nerve is injured during the operation and there is aphonia, which usually disappears in a month. Occasionally there is uncontrolled hemorrhage, especially in the infected cases.

The *indications for operation*[101] include:

1. Evidence of diminished cardiac reserve or of heart failure as indicated by undue fatigue or dyspnea on exertion, orthopnea, peripheral edema and venous engorgement, or a history of previous attacks of heart failure.
2. Evidence of a large circulatory shunt or of cardiac strain as indicated by pronounced enlargement of the heart, pulmonary congestion or a high pulse pressure.
3. Definite underdevelopment due to a diminished peripheral circulation, but this is an uncommon indication.

Inasmuch as many cases of patent ductus with superimposed bacterial endarteritis were cured by ligation of the ductus, this complication was numbered among the indications for the operation. However, the relatively high operative mortality rate coupled with the brilliant results of antibiotic therapy have led me to institute the latter treatment before resorting to operation. Ligation may be undertaken if (a) a satisfactory clinical response is not obtained with penicillin or streptomycin, or (b) after the bacterial infection is controlled in order to prevent recurrent infection or heart failure.

According to one viewpoint all children with patency of the ductus arteriosus should undergo the corrective operation whether or not there is evidence of cardiac embarrassment because of the otherwise poor prognosis, and because of the remarkable improvement of these patients even when there did not previously appear to be any significant clinical disturbance. These arguments become more and more cogent as the operative risk is diminished. Among adults with patent ductus, section or ligation of the ductus should be performed only if there is distinct evidence of circulatory strain or failure.

Ligation or section of the ductus arteriosus is contraindicated when this anomaly is associated with other congenital cardiac defects for which the ductus circulation is a compensation. This group can usually be distinguished by the presence of cyanosis, and, if doubtful, with the aid of angiocardiography and intracardiac catheterization. Since these complicated cases usually succumb before the age of three, ligation of the ductus is almost always deferred to the age of four or more.

Persistent Truncus Arteriosus Communis

Closely related to patency of the ductus arteriosus are the cases with a common arterial trunk, instead of distinct aorta and pulmonary artery, due to defective development of the bulbar septum. If the pulmonary arteries arise directly from the truncus arteriosus, cyanosis is absent or minimal. More often the circulation through the lungs is by way of dilated bronchial arteries; in such

cases cyanosis is usually intense as the pulmonary circulation and oxygenation are deficient. In both cases there is a harsh systolic murmur and thrill and cardiac enlargement. Roentgen ray examination discloses a characteristic shelf-like projection to the anterior chest wall in the left anterior oblique view, a widened aortic shadow and absence of the contour of the pulmonary conus.[47] If the pulmonary blood supply is by way of the bronchial arteries and a rudimentary pulmonary artery of sufficient size can be found, considerable clinical improvement results from anastomosis of a systemic artery (aorta, innominate or subclavian) to the pulmonary artery (p. 656).

Rarely a persistent truncus arteriosus is associated with a single ventricle.[200]

Aortic Septal Defect—Aneurysm of Sinus of Valsalva

There is a small opening between the aorta and pulmonary artery about 1 cm. above the semilunar valves. The symptoms and signs may be insignificant or ill-defined, or may resemble those of a patent ductus arteriosus. In other cases the septum between the vessels is extremely thin leading to an aneurysm of the right sinus of Valsalva or more rarely of the posterior sinus.[150, 132] These aneurysms may become clinically significant because of a tendency to perforation with a consequent defect between the right aortic sinus and the right ventricle (pulmonary conus) or pulmonary artery or between the posterior aortic sinus and the right atrium.[99] With perforation, the symptoms and signs resemble those of patency of the ductus, but the murmur and thrill appear more superficial, the murmur is situated lower (third or fourth left interspace) and there is more pronounced cardiac enlargement.

The diagnosis is suggested by the sudden occurrence without apparent cause, except exertion occasionally, of symptoms of progressive heart failure and signs of a communication between the aorta and right side of the heart (continuous or harsh systolic murmur and thrill). In a personal case of sinus aneurysm with rupture into the right atrium, correctly diagnosed ante mortem, there were in addition to the sudden appearance of the murmur and thrill, progressive congestive heart failure, the development of right axis deviation not present in earlier electrocardiograms, high pulse pressure and Corrigan pulse and a characteristic double pulsation in the cervical veins and over the liver.

Death may occur suddenly[109] or within a few months or years, but Abbott[1] has reported a case of survival for nine years after the perforation. Bacterial endocarditis may complicate the lesions of the aortic septum, or be the cause of aneurysm of the sinus with rupture (p. 782).

Coarctation of the Aorta

Since Bonnet's[24] description, two forms of coarctation of the aorta are generally recognized, the infantile and the adult. As implied by these names, the infantile form usually occurs in infants and is soon fatal, while subjects with the adult form often reach mature life. Exceptions occur in that the infantile form is encountered occasionally in adults and the adult form in subjects who die during infancy and childhood. The *infantile form* is characterized by diffuse involvement of the aortic isthmus (from the origin of the left subclavian artery to the insertion of the ductus arteriosus), by the association of other congenital anomalies including a patent ductus and by cyanosis. The *adult form* is characterized by a more localized constriction at or below the insertion of the ductus,

by the absence of serious cardiac anomalies (except bicuspid aortic valve or subaortic stenosis), by a closed ductus and by the absence of cyanosis.

Sex Incidence. There is a striking preponderance of males (4 to 1 or 5 to 1) among patients with coarctation of the aorta.

Embryology and Pathology. The aorta in fetal life may be considered as divided into two functional units, the upper one extending from its cardiac origin to the insertion of the ductus at the lower end of the arch (i.e., the isthmus), and a lower portion beginning at the insertion of the ductus and including the remainder of the descending aorta. The upper unit receives the more oxygenated blood which, arriving in the right atrium from the placenta and inferior vena cava, is directed by the sinus valve through the foramen ovale to the left side of the heart and ascending aorta. This oxygenated blood supplies the head, the heart and the upper extremities. Because this circuit contains only about half the venous return, it may be presumed that the aortic pressure is only sufficient to supply the upper unit and that the blood flow in this upper unit does not extend significantly beyond the isthmus. The low pressure at the termination of the upper unit may account for the normal narrowing at the isthmus of the aorta.

The unoxygenated blood from the superior vena cava, after relatively little mixing with the oxygenated blood in the right atrium, is directed to the right ventricle, pulmonary artery and thence through the ductus arteriosus into the lower unit of the aorta. This division of the circulation has recently been demonstrated roentgenographically in sheep fetuses, after the injection of radiopaque material into the inferior and superior vena cava, respectively.[12] Furthermore, the division into upper and lower units of the aorta may be an anatomic as well as a functional one, for there are cases in which the aortic arch and isthmus, supplied by the left ventricle, are completely severed from the descending aorta beyond the isthmus, this unit receiving blood from the right ventricle through the ductus arteriosus.[67]

According to a theory which I have proposed, *adult coarctation of the aorta,* unlike the infantile form, is a late fetal or a neonatal anomaly.[74] It occurs after and is due to closure of the ductus arteriosus. Normally an adequate pressure in the upper unit of the aorta prevents the constriction of the aorta at its ductal insertion when the ductus closes. In instances of "adult" coarctation this constriction occurs because the aortic pressure in the upper unit is, at the time of ductus closure, insufficient to maintain the continuity between upper and lower aortic units. This may be due to maldevelopment of the aortic valve and left ventricle as suggested by the frequent association of bicuspid aortic valve and subaortic stenosis.

The *infantile type of coarctation is probably an early, primary developmental anomaly of the fourth left aortic arch,* occurring in the second month of fetal life. Thus this lesion, unlike the usual adult type, is associated with other developmental anomalies such as a septal defect or transposition of the arterial trunks. Whatever the mechanism, the blood flow and pressure in the upper unit of the aorta is low, leading to an exaggeration of the normally slight narrowing of the isthmus and to hypoplasia of the entire upper portion of the aorta. Furthermore, this low aortic pressure leaves an unusually high pulmonary blood flow and pressure so that even when the lungs develop, there is enough of a pulmonary pressure to keep the ductus open. Hence patency of the ductus arteriosus almost always accompanies an infantile coarctation.

The *heart* reveals hypertrophy of the left ventricle in all cases. The adult form of coarctation is not infrequently associated at necropsy with a bicuspid aortic valve which may be congenital or rheumatic (p. 777). Congenital subaortic stenosis and aortic insufficiency occur occasionally in cases of adult coarctation, with or without bicuspid valves. Miliary aneurysms of the small cerebral vessels are not infrequent, especially at their bifurcation in the region of the circle of Willis. Forbus[70] found the media of the vessels at the site of the aneurysm either very thin or absent. The cerebral aneurysms may be due to the high tension in the upper half of the body (including the brain) which appears in infancy, rather than to a developmental defect.

Schwartz and Greene[183] described cases of coarctation of the aorta in children with involvement of the origin of the left subclavian. An atypical form of coarctation of the aorta has been described in which the left subclavian artery is occluded, but there is no obstruction of the blood flow in the thoracic aorta. Almost complete absence of the left radial pulse and a slow rise in pulse tracings were characteristic. The diagnosis can be confirmed by angiocardiography.[88]

Pathologic Physiology in Adult Coarctation of the Aorta. There is a normal blood flow from the right side of the heart through the lungs and from the left ventricle into the aorta. The blood flow to the head and upper extremities is normal or elevated.[18] But because of the aortic constriction, aortic blood to the lower half of the body is detoured. A striking *collateral circulation* develops around the constriction in cases of adult coarctation. Branches of the subclavian artery above anastomose with branches of the descending aorta below the stenosis or occlusion. The chief anastomoses are between: (1) the superior intercostal branches of the subclavian artery and the first intercostal branches of the aorta within the thorax, (2) the scapular branches of the subclavian artery and the aortic intercostal vessels in the chest wall, (3) the internal mammary branches of the subclavian and the epigastric branches of the external iliac in the abdomen. These anastomotic vessels become greatly dilated and the aortic intercostal vessels often erode the lower margins of the ribs posteriorly. The collateral circulation may be limited to the interior of the chest wall and thus not visible or palpable clinically.

Detailed reviews of the anatomic and clinical features of coarctation of the aorta have been presented by Abbott,[2] Blackford,[20] King,[113] Lewis,[123] Bramwell,[26] and Reifenstein et al.[165]

Clinical Features. *Symptoms* are often absent. The patient may be unaware of his disease until there is a sudden fatal complication such as rupture of the aorta or of a cerebral vessel or until cardiac failure or bacterial aortitis develops. Certain symptoms may be associated with the hypertension which is usually present. These include *headaches,* dizziness, tinnitus, insomnia, epistaxis and nervousness. Neurologic symptoms may be the first manifestations due to cerebral complications (see below). The patient may complain of weakness, coldness, pallor, numbness or cramps in the legs due to diminished circulation in the lower half of the body. Occasionally there is intermittent claudication. The temperature of the feet has been found diminished.[192] *Symptoms of congestive heart failure,* especially dyspnea, may eventually result from the hypertension and left ventricular enlargement. Occasionally there is palpitation and precordial distress.

The *objective signs* are more striking and of diagnostic importance. The

subjects with adult coarctation are often robust, muscular and intelligent. There are striking bilateral supraclavicular pulsations due to large subclavian arteries. Dilated, tortuous *collateral vessels* may be visible or palpable. Most often these are situated along the inner borders of and across the scapula, in the axilla or less often along the sternum or in the epigastrium. The vessels are more readily observed when the subject is in a warm room or has been active. According to Campbell and Suzman,[36] these collateral vessels are more readily observed if the patient leans forward. Systolic bruits and thrills may be present over these dilated collateral vessels. Cyanosis and clubbing are absent in the adult type of coarctation because there is no venous-arterial shunt and the pulmonary blood flow is normal.

Physical examination of the heart may reveal only a slight enlargement to the left and downward. There is usually a moderately loud systolic murmur over the precordium, most intense at the base, but often heard also in the left interscapular region. The murmur is occasionally loud and harsh and accompanied by a thrill. Sometimes it is louder in the back than anteriorly. The murmur may arise in the dilated collateral vessels or at the site of constriction of the aorta. There may also be murmurs of an associated subaortic or aortic stenosis and insufficiency.

Arterial Pulses. In contrast with the strong pulsations in the suprasternal and supraclavicular regions, there is no palpable aortic pulsation in the abdomen. The femoral pulses are weak or impalpable. The circuitous course of aortic blood flow to the femorals not only weakens the femoral pulse but also causes it to appear later than the radial pulse when simultaneous graphic records are made (Fig. 68*C*). Normally the femoral pulse slightly precedes the radial.

Hypertension in Coarctation of the Aorta. Hypertension is a characteristic feature of the adult type of aortic coarctation. It may be absent if the anomaly is complicated by heart failure, bacteremia and, according to King,[113] occasionally in uncomplicated cases. The hypertension is chiefly systolic, but the diastolic pressure may also be elevated to a variable degree. A diagnostic feature is the limitation of the hypertension to the upper extremities, the blood pressure in the lowers being normal or depressed. Normally the systolic blood pressure in the femoral artery is about 20 mm. higher than in the brachial. In cases of adult coarctation the brachial systolic pressure is considerably higher than the femoral systolic. The arterial blood pressure in the upper and lower extremities has been measured directly by cannulization of the vessels and recorded by optical tracings.[218, 190, 31] These measurements revealed that while the systolic blood pressure was higher in the upper than in the lower extremity, the diastolic pressures were equal or only slightly less in the lower than in the upper extremity. The femoral systolic pressure was depressed but the femoral diastolic was usually slightly above normal. From these observations Steele[190] concluded that the increased peripheral resistance underlying the hypertension is generalized and involves lower as well as upper extremities. However, Bing and his associates[18] found the diastolic pressure elevated in the arms and not in the lower extremities and concluded that there was no *generalized* elevation of peripheral vascular resistance.

Clinical studies of circulatory dynamics in cases of coarctation of the aorta[23] and animal experiments[151] have failed to elucidate the exact mechanism responsible for the hypertension and its limitation to the upper half of the body.

The *mechanical theory* supposes that these abnormalities are purely the result of mechanical obstruction, but persistent hypertension has not been produced experimentally in dogs by occluding the aortic isthmus at a level corresponding to the site of human adult coarctation. The *humoral theory* proposes that the hypertension is due to renal ischemia. It is supported by studies of renal blood flow[75] and by the experiments in which hypertension in dogs[82] and in rabbits[179] was produced by means of constricting the aorta just above both renal arteries. Hypertension did not follow similar obstruction below the origins of these vessels. On the other hand, the blood pressure in these experiments gradually fell to normal unless the aorta was clamped below as well as above the level

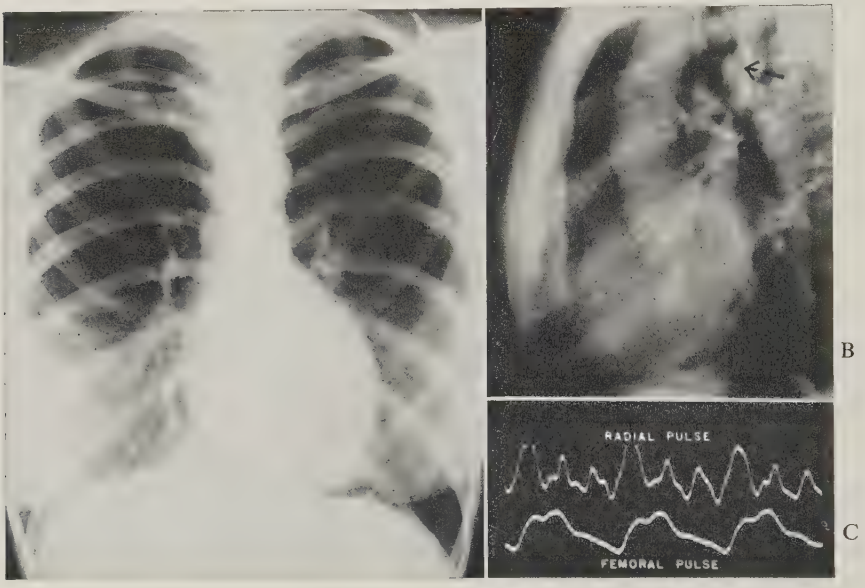


Fig. 68. Coarctation of aorta. *A*, Notching of lower borders of ribs.
B, Angiocardiogram, left lateral position. Visualization of ascending aorta and arch. At and beyond aortic isthmus irregularity and narrowing of aortic lumen (arrow).
C, Simultaneous radial and femoral pulse to show delay of latter.

of the renal vessels. Another discordant observation is the case reported by Maycock[131] in which there was pronounced brachial hypertension although the stenosis was below the level of the renal vessels. The observations of Bing et al.[18] (supra) and those of Hull[102] also indicate that the hypertension is not due to renal ischemia and a consequent humoral pressor substance, but to the resistance of the aortic stenosis and the collateral vessels.

Roentgenology. The heart is only slightly enlarged, the enlargement involving the left ventricular contour as in cases of essential hypertension.

The ascending aorta is dilated and bulges somewhat to the right.

The aortic knob in the anteroposterior view is often small and may be absent. According to Fray[72] a pathognomonic feature is the presence of a localized defect or break in the continuity of the aortic arch on its convexity, as viewed in the left anterior oblique view. This break is situated at the junction of the transverse and descending portion of the arch and corresponds to the location

of the coarctation at the point of insertion of the ligamentum arteriosum. Gladnikoff[80] emphasized the recognition of a dilated left subclavian artery, medial displacement of the aortic arch and indentation in the upper portion of the descending aorta as signs of coarctation.

Of at least equal diagnostic value, and more readily discoverable, is the *erosion of the lower borders of the ribs* by the large collateral vessels, first noted roentgenoscopically by Railsback and Dock[163] (Fig. 68*A*). The erosions may involve a variable number of ribs from the third to the tenth, usually on both sides and in their posterior portion. The erosions are localized, smooth and curvilinear. Because many years are required for the collateral vessels to enlarge sufficiently to erode the ribs, the erosions are usually absent in young children.

The normal curve of the barium-filled esophagus may be absent, and the esophagus, when viewed in the right anterior oblique position, may be seen to be situated to the right of the aortic arch.

Angiocardiography. By intravenous cardiography with the aid of diodrast, successive films show distinctly the site of occlusion or stenosis of the aorta and often its approximate length and caliber may be estimated[86] (Fig. 68*B*). Preoperative demonstration of its relation to the left subclavian artery by this means is of value to the surgeon. At the same time angiocardiography may disclose the presence of associated congenital vascular lesions and the state of the collateral circulation, particularly the size of the internal mammary arteries and the aortic branches proximal to the coarctation. Nicolson[149] reported a case of coarctation of the aorta with arrested bacterial endocarditis in which a calcified mycotic aneurysm at the site of constriction was clearly filled by contrast medium. *Thoracic aortography* has also been employed to demonstrate the coarctation.[30] An F7 or F9 catheter is inserted through the upper part of the exposed radial artery into the subclavian artery or aortic arch and 50 cc. of 70 per cent diodrast rapidly injected while roentgen ray films are made. The ulnar artery has also been used.[222]

Electrocardiogram. This is not diagnostic. There may be a left axis deviation.

Diagnosis. The diagnosis of coarctation of the aorta is discussed independently of the general diagnosis of congenital heart disease because the disease is often masked as essential or malignant hypertension, neurologic disease or cardiac failure without suggesting the possibility of a congenital cardiac abnormality. Therefore the finding of hypertension, particularly in a young adult or child, should always be followed by palpation of the femoral pulse and determination of the femoral blood pressure. If the femoral pulse is weak or absent and the blood pressure less than in the upper extremity, a tentative diagnosis of coarctation of the aorta is warranted. Confirmatory signs are then sought, e.g., visible or palpable collateral vessels over the scapular and interscapular regions, the axilla, parasternal or lower anterior chest wall, murmurs or thrills in these areas, particularly a systolic murmur which is as loud or louder in the interscapular region as over the precordium, roentgenologic observation of erosion of the ribs or defect in the aortic arch. Eisenberg[62] emphasizes the fact that in children with the adult form of coarctation, there may be no great collateral circulation and no erosion of the ribs. Diagnosis in such cases depends essentially on the difference in brachial and femoral blood pressures, on weakness or absence of the femoral pulse and on confirmation by angiocardiography.

Coarctation of the aorta should also be considered in cases of cerebral accidents in young persons.

Occasionally a loud interscapular murmur or the presence of large collateral vessels suggests the diagnosis of coarctation in the rare cases of coarctation without hypertension.

A simultaneous recording of femoral and radial pulse waves revealing a lag in the former, and delayed build-up of the femoral pulse, also confirm coarctation of the aorta.[123, 218]

The finding of unequal radial pulses, with weakness or absence of the left brachial and radial, should suggest the possibility of coarctation. The latter should also be sought in cases of congenital subaortic stenosis.

Prognosis, Complications and Cause of Death. A knowledge of the outlook for untreated cases of coarctation has assumed increased importance since a technic of surgical treatment has been developed.

The adult form of coarctation is occasionally compatible not only with long life[166] (Reynaud's patient lived to the age of ninety-two) but often also with normal physical activity. Nevertheless, in reported series of cases death occurred at a relatively early age and in most instances before the fortieth year.[2] In Blackford's[20] series of 323 cases, only 68 patients survived the age of forty; 125 died in the first year, 142 (including the former 125) died in the first decade, and 112 between the ages of sixteen and forty. This series included cases of the infantile as well as of the adult form of coarctation. In a more recent study of 104 cases of the adult type of coarctation of the aorta, 61 per cent died during or before the fortieth year of life and the average age at death was thirty-five.[165] But about 25 per cent of the patients attained a relatively normal life span and died of incidental causes. It is probable that these series include the most severe cases of coarctation and that those with the least disability and complications and with the longest life are either overlooked or treated by the general practitioner; the latter, therefore, frequently do not enter into hospital and autopsy statistics. Nevertheless, the overall outlook for a normal life appears to be poor.

The commonest *complications* and *causes of death* are congestive heart failure, bacterial endocarditis or aortitis, rupture of the aorta and cerebral hemorrhage (exclusive of that due to bacterial embolism).

Progressive cardiac failure occurred in 25 per cent of Abbott's[2] 200 cases and sudden cardiac death in 8 per cent. Aside from hypertension, congenital subaortic stenosis, rheumatic cardiovalvular disease, coronary arteriosclerosis and myocardial infarction are contributory factors in the development of the heart failure.

Rupture of the aorta was the cause of death in 23 per cent of cases in the series of Reifenstein et al.[165] This appears as a linear or zigzag tear, usually 1 to 4 cm. above the aortic valve, or just below the site of the coarctation. Microscopic examination of the ascending aorta reveals defects, splitting and disorientation of the elastic tissue in the media possibly due to prolonged mechanical stress.[61] The upper aortic rupture produces a dissecting aneurysm of the descending aorta which may rupture into the pericardium and cause fatal cardiac tamponade. Rupture at the lower site is into a bronchus, esophagus or left pleural cavity.

Cerebral accidents are responsible for death in 10 to 17 per cent of reported series of cases. Subarachnoid or cerebral hemorrhage results from perforation of cerebral miliary aneurysms, probably of congenital origin.[9] Hemorrhage

and encephalomalacia may also be caused by mycotic emboli and aneurysms of the cerebral vessels secondary to a bacterial endocarditis or aortitis. Headache, convulsions, hemiplegia, coldness and numbness in the lower extremities, vertigo, tinnitus and transitory visual disturbances are among the more common neurologic manifestations of coarctation of the aorta.[217] In some cases a minute perforation of a cerebral miliary aneurysm with intermittent leakage of blood has been diagnosed on the basis of recurrent apoplectiform seizures occurring suddenly, associated with severe, bursting headache and followed by transient neurologic signs.[49]

Bacterial endocarditis most commonly involves the aortic valve, which is often bicuspid, or the site of congenital or rheumatic stenosis and insufficiency. A similar clinical picture results from a *bacterial aortitis* in which the bacterial vegetations are situated in the aortic intima just below the site of the coarctation or occasionally in the ascending aorta.

Surgical Treatment. Successful correction of coarctation of the aorta was first accomplished independently by Crafoord and Nylin[45] and by Gross and Hufnagel.[94] There were 3 deaths in a series of 23 cases reported by Bing, Blalock et al.,[18] 2 deaths in a series of 32 cases resected by Crafoord,[44] and 7 deaths among 60 cases reported by Gross.[92] After the application of special clamps above and below the constricted portion of the aorta, the latter is ligated and resected and the continuity of the artery reestablished by end-to-end anastomosis.[92, 79] When this is not feasible, the left subclavian artery may be sectioned,[40, 25] its distal portion ligated and its proximal end anastomosed with the aorta which has previously been sectioned distal to the coarctation. A continuous mattress silk suture with an everting type of repair is less apt to cause later aortic dissection than an anatomic layer-to-layer anastomosis.[92] After the anastomosis has been effected, the clamps on the aorta and subclavian artery must be removed gradually in order to prevent sudden flooding of the vascular bed and acute cardiac dilatation. There is a rapid reduction in the hypertension in a few days or a more gradual reduction within two weeks after the operation. Simultaneously there is a restoration of normal pulsations in the lower extremities.

On the basis of reported studies revealing a very poor prognosis for untreated coarctation (supra), one should conclude that surgical correction will be indicated in the great majority of cases. However, it is probable that with further study the indications for surgical treatment in the individual case will become more sharply defined. Experience to date suggests that the optimum time for operation is between the ages of six and twenty. Beyond the latter age the aorta exhibits regional atherosclerosis of sufficient degree to impair the ease and safety of surgical manipulation. Nevertheless surgical resection and anastomosis has been effected in patients beyond the age of thirty.

OTHER CONGENITAL CARDIAC ANOMALIES

Right-Sided or Double Aortic Arch

Embryology and Pathology. In the five weeks embryo there are six pairs of aortic arches connecting the primitive ventral and dorsal aorta. The first two disappear, but their ventral roots form the external carotid arteries. The third arches form part of the internal carotid arteries. The right fourth arch normally disappears, but its ventral root forms the innominate artery. The left fourth arch forms the arch of the adult aorta. The fifth arches disappear. The sixth

arches also disappear but the ventral root on the right forms the pulmonary artery and the dorsal root on the left forms the ductus arteriosus.

A persistent right-sided aortic arch is found when the fourth left arch disappears while the fourth right embryonic arch develops into the adult arch of the aorta.[14] The right aortic arch may be associated with an aorta which descends on the right side of the esophagus and spinal column, or with a left descending aorta when the latter crosses over the right bronchus and behind the esophagus and trachea to reach its normal diaphragmatic opening. The aorta crosses to the left when it is drawn over by a ductus arteriosus or a left subclavian artery which arise in their normal left-sided pattern. Occasionally both fourth arches persist and give rise to a double aortic arch encircling the trachea and esophagus.[5]

The right-sided aortic arch occurs most often in association with the tetralogy of Fallot and other conditions in which there is dextroposition of the aorta. It is seen more commonly in males.

Clinical Features. As a rule, a persistent right aortic arch or double aortic arch is clinically insignificant and is discovered accidentally by roentgen ray examination or at autopsy. But it may become of clinical importance in three ways:

First, it occasionally produces symptoms, such as *dysphagia and dyspnea,*[139] by compression of the esophagus or trachea at about the level of the third dorsal vertebra (dysphagia lusoria). These abnormal vascular structures are sometimes termed "vascular rings," since they encircle the trachea and esophagus. Esophageal pressure may be caused not only by a right or double aortic arch, but also by a diverticulum formed from the vestige of the fourth left arch, by a left subclavian artery arising abnormally from a persistent right aortic arch, by a ductus botalli which runs behind the esophagus, and by a right subclavian artery arising abnormally from the left descending arch. Brean and Neuhauser[28] reported findings in 15 children with an aberrant right subclavian artery, running obliquely upward and to the right from the extreme left side of the aortic arch. It compressed the esophagus and produced a characteristic oblique extrinsic filling defect in the posterior wall as demonstrated by roentgen rays when the esophagus contained barium. The term *arteria lusoria* has been applied to these abnormally situated vessels which may cause dysphagia. In the cases in which the descending aorta crosses to the left, attacks of croup and pulmonary infections are common in infancy and early childhood, and brassy cough may result from compression of the left recurrent laryngeal nerve. Noisy, stridulous breathing, mild dysphagia, chronic cough and recurrent pulmonary infections are not infrequent in the cases in which a double aortic arch together with an aberrant left subclavian or patent ductus or ligamentum arteriosum form a vascular ring around the trachea and esophagus.[196]

Second, the right-sided aortic arch, especially when associated with pressure symptoms, has been diagnosed incorrectly as a mediastinal tumor, lymphoma or aneurysm[171] leading to the unwarranted administration of radiotherapy or to surgery.

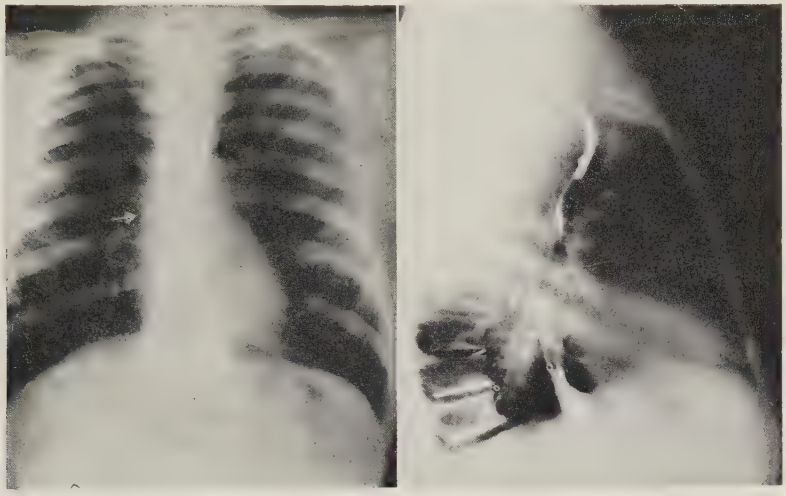
Third, the possibility of these vascular anomalies and the close relationship of these aberrant vessels to the trachea and esophagus must be borne in mind when bronchoscopy or esophagoscopy is considered or when surgical correction of tetralogy of Fallot is contemplated.[95]

The *diagnosis* is made by *roentgen ray examination* (Fig. 69). There is a

pulsating shadow of the right aortic arch along the right border of the upper sternum and trachea, extending to the right sterno-clavicular joint. On the other hand, the aortic knob on the left is either missing or, in cases of double aortic arch, the left knob is small. The trachea is slightly displaced to the left and in lateral views is seen to be narrowed. The barium-filled esophagus is seen to be distinctly displaced to the left and indented. This displacement distinguishes cases of right aortic arch from coarctation of the aorta and other congenital cardiac lesions associated with a small or absent aortic knob.

In cases of right aortic arch with left descending aorta the barium-filled esophagus is displaced forward and is characteristically kinked (Fig. 69*B*).

Angiocardiography portrays clearly the anatomic abnormalities of the aortic arch.



A B

Fig. 69. Right aortic arch. *A*, Posteroanterior view. Absence of aortic knob on left. A shadow is seen extending along right side in supra cardiac area and caudad to right of spine (arrow).

B, Right lateral view. Barium-filled esophagus displaced anteriorly by right aortic arch.

The diagnosis of a compressing vascular ring should be suspected in any infant with stridor, cough or dysphagia and frequent respiratory infections.

Treatment. Relief of the compression symptoms caused by a vascular ring of anomalous aortic arch and branches has been effected by severance of the smaller anterior aortic arch.[91] Section of a persistent malposed cord of the ligamentum arteriosum or of an anomalous left or right subclavian artery can also be performed if these are responsible for symptoms of tracheal or esophageal constriction.

Dextrocardia

Rarely the heart is situated outside the thoracic cavity, either in the abdomen or even outside the chest wall. This is termed ectopia cordis. The condition is almost always fatal in a few days or in a month or so. Occasionally patients with ectopia cordis abdominalis survive into adult life. Pectoral ectopia cordis through a fissure in the lower sternum permits viability if both pericardial layers are intact.

True dextrocardia consists of a mirror-like transposition of the heart so that the left chambers and apex are on the right and the right chambers are on the left, the apex being formed by the left ventricle. There is a similar mirror-like transposition of the other viscera (situs inversus), the spleen being on the right and the liver on the left. There are no symptoms; the condition is without clinical significance except in so far as it may complicate abdominal diagnosis. However, there appears to be an increased incidence of severe bronchiectasis and sinusitis in cases of dextrocardia and situs inversus.[3, 178]

True dextrocardia with situs inversus may be recognized by physical examination, roentgenologically and by the electrocardiogram.

Physical examination discloses the apical impulse on the right, hepatic dullness on the left and the tympany of Traube's space on the right.

Roentgen ray examination reveals the heart chiefly in the right chest with a mirror transposition of the silhouette so that the anterior view of the chest resembles the normal posterior view. The stomach bubble is on the right side and the right leaf of the diaphragm is lower than the left.

In the electrocardiogram, lead I is a mirror image of the normal lead I, the P, QRS and T waves are all inverted. Lead II is identical with the usual lead III and lead III with the usual lead II. If the leads to the arms are reversed, a normal electrocardiogram is obtained. For this reason, whenever the electrocardiogram is that of dextrocardia, it should be repeated to be sure that it was not due to improper connection of the leads. Special problems arise in the interpretations of electrocardiograms when coronary occlusion or other cardiac disturbances are associated with situs inversus.[185]

Occasionally there is an isolated, true dextrocardia, the abdominal viscera retaining their usual position.[173, 126, 177] This form of dextrocardia is almost always accompanied by other cardiac anomalies which may be of a serious nature, e. g., especially cor triloculare biatrium, but also pulmonary stenosis or atresia, and other conditions which produce persistent cyanosis. A persistent left aortic arch is often associated. There are also cases of false congenital dextrocardia in which there is no mirror transposition, the heart being merely displaced and rotated so that it lies in the right side of the chest. But the left chambers are on the left and the right chambers are on the right and posterior. There are almost always serious associated cardiac anomalies which determine the clinical course, e. g., transposition of the great vessels, pulmonary atresia, right-sided aortic arch, and defects or absence of the cardiac septa (cor biloculare). There may also be extracardiac anomalies such as congenital defects of the ribs or pectoral muscles, or herniation of the lungs.

Dextroversion and dextrocardia are terms applied sometimes to cases in which the heart is displaced into the right chest by some external and usually acquired disturbance involving the lungs or pleura.

Congenital Idiopathic Hypertrophy

So-called congenital idiopathic hypertrophy is probably not a specific anomaly but includes a variety of conditions. These have been discussed (p. 548). When enlargement of the heart is observed in infants or young children, the various congenital defects of the heart and great vessels discussed above, and infections, anemias or B avitaminosis, and von Gierke's disease (p. 959) must be excluded as possible etiologic factors.

CONGENITAL VALVULAR DEFECTS

Congenital valvular defects are relatively common in association with one or more of the anomalies already discussed. But except possibly for the bicuspid aortic valve, they are rare as isolated lesions.

Pulmonary Stenosis

This is the most common congenital valvular lesion. It occurs usually as part of the tetralogy of Fallot or combined with a ventricular septal defect. Infundibular stenosis is a narrowing of the pulmonary conus, resulting from failure of expansion of the bulbus cordis to form the right ventricle.[56] It is rare as an isolated lesion. Stenosis of the pulmonary valve is characterized by a dome-like fusion of the pulmonary cusps with a central perforation or by scarring and narrowing of the pulmonary annulus and leaflets. It is occasionally observed as an isolated lesion.[73, 46] The pulmonary artery is usually dilated beyond the stenosis and the right ventricle is hypertrophied. The foramen ovale may be secondarily reopened as a result of the elevated pressure in the right atrium and a venous-arterial shunt eventually develops.

At first the disease is asymptomatic. Later fatigability and dyspnea on exertion or in paroxysms are the common symptoms. Cyanosis is absent unless there is a patent foramen ovale. In the latter circumstance cyanosis develops late, as the right auricular pressure rises and causes a venous-arterial shunt. Eventually clubbing of the extremities and polycythemia appear in these cases. Congestive heart failure (involving predominantly the systemic circulation) develops in the third or fourth decade and is the chief cause of death. Pulmonary infections including tuberculosis are relatively more common than in association with other congenital lesions.[7] Bacterial endocarditis occurs occasionally.

There is a rough long systolic murmur, maximal in the second left interspace near the sternum, transmitted toward the left cervical region and occasionally to the back. A systolic thrill is often heard in the region of the murmur. The second pulmonic sound is weak or absent.

The *roentgen ray examination* reveals enlargement of the right border, prominence of the pulmonary artery and conus and great enlargement of the right ventricle in oblique views. In cases of pulmonary stenosis with patent foramen ovale the combination of cyanosis and post-stenotic dilatation of the pulmonary artery requires differentiation from the Eisenmenger syndrome.[184a] The Blalock operation may be indicated in the former and not in the latter.

Angiocardiography usually outlines clearly the stenosis at or near the pulmonary valve.

The *electrocardiogram* shows a pronounced degree of right axis deviation. Sometimes there is inversion of the T wave in lead III or leads II and III. Right bundle branch block has been reported.[21]

A bicuspid pulmonic valve may be present in cases of pulmonary stenosis. Rarely there is a congenital pulmonary insufficiency. When the pulmonary insufficiency occurs in connection with a stenosis of the pulmonary valve, there may be a diastolic as well as a systolic murmur along the left border of the upper sternum.

A complete pulmonary obstruction (*pulmonary atresia*) is less common

than a pulmonary stenosis. It is usually part of the tetralogy of Fallot. If the ventricular septum is closed, pulmonary atresia is associated with a patent ductus arteriosus and sometimes also with a patent foramen ovale. The blood then passes from the right ventricle to the dextroposed aorta and thence in part to the systemic circulation and in part to the lungs by way of the ductus arteriosus. Death usually occurs when the ductus undergoes its normal obliteration, but rarely a sufficient collateral circulation develops and maintains life for a brief period. Extreme cyanosis is present from birth. Dyspneic attacks recur and may be fatal. If the associated dextroposition of the aorta is not extreme and a rudimentary pulmonary vessel of sufficient size can be found, the Blalock-Taussig operation may be successful (p. 656).

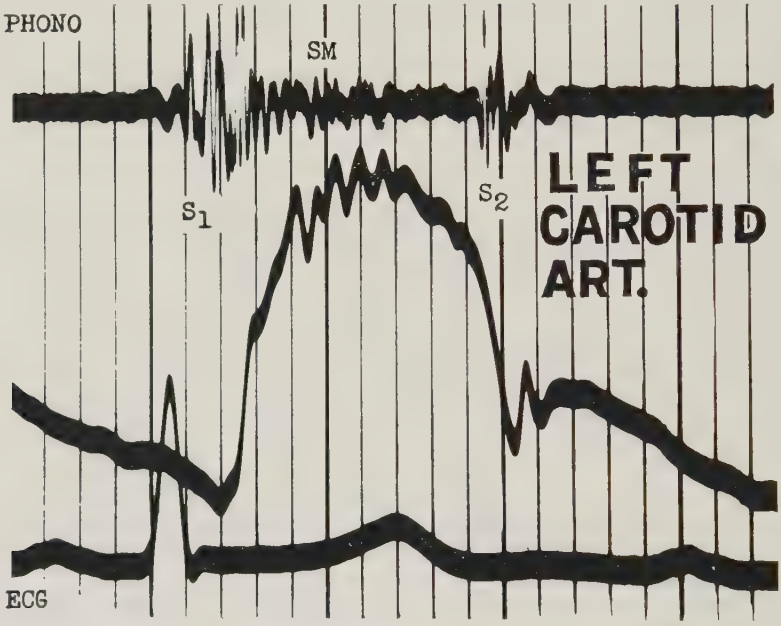


Fig. 70. Subaortic stenosis. Phonocardiogram and carotid artery tracing. Prolonged, high amplitude, systolic murmur. Anacrotic carotid pulse with systolic vibrations and plateau.

Treatment. Promising results have been reported in the surgical treatment of the purely valvular pulmonary stenosis. A valvulotome was inserted through an incision in the right ventricle; the pulmonary valve was divided and the orifice enlarged with a dilating forceps.[29a]

Aortic Valvular Disease

A *bicuspid aortic valve* alone or in combination with other lesions, such as coarctation of the aorta or subaortic stenosis, is not infrequent. It is uncertain how often the bicuspid aortic valve is of congenital and how often of rheumatic origin (p. 777). Its chief significance is the frequency of a complicating bacterial endocarditis.

Aortic valvular stenosis is usually stated to be rare,[209] but my personal clinical and pathologic observations suggest otherwise. Grishman and his associates[87] recently reported 23 cases of congenital aortic or subaortic stenosis.

Aortic stenosis is often due to a firm, raised endocardial ring of fibrous tissue a few millimeters below the aortic valve. This is known as *subaortic stenosis*. This may be associated with a second stenosis of the valve itself, so-called double aortic stenosis.[32] A post-stenotic dilatation of the aorta may occur similar to the post-stenotic dilatation of the pulmonary artery in pulmonic stenosis. Coarctation of the aorta, narrowing of the aortic isthmus and bicuspid aortic valve are not infrequently associated. Subaortic stenosis probably represents an arrest of involution of the bulbus cordis.[110] The left ventricle becomes hypertrophied.

There may be distinct underdevelopment with severe stenosis (aortic dwarfs). There is a loud harsh systolic murmur and thrill, maximal in the second right interspace or Erb's point and radiating to the cervical region (Fig. 70). But the murmur may be heard lower over the sternal region or toward the apex. There may be an associated diastolic murmur. The second aortic sound may be distinct, weak or absent.

Roentgen ray examination reveals a large left ventricle and slight prominence of the ascending aorta, due to post-stenotic dilatation.

Electrocardiography discloses left axis deviation.

Pulse tracings over the cervical arteries show a characteristic slow initial rise, an anacrotic notch, systolic vibrations and a systolic plateau (Fig. 70).

In many cases the clinical course is asymptomatic but not infrequently death has occurred relatively early because of a complicating bacterial endocarditis or congestive heart failure.

The *diagnosis* is based on the history or finding of a harsh systolic murmur and thrill in childhood, the absence of cyanosis and left axis deviation of the electrocardiogram. The characteristic carotid pulse tracing is diagnostic of aortic or subaortic stenosis regardless of etiology.

Aortic atresia is rare.[199, 187a] The left ventricle is hypoplastic or nonfunctioning and oxygenated blood from the left atrium reaches the right atrium through a defect in the auricular septum. Mixed venous and arterial blood passing from the right atrium to the right ventricle and pulmonary artery reaches the aorta by way of a patent ductus. Intense cyanosis, dyspnea, great right-sided cardiac enlargement and early death characterize the clinical picture.

Tricuspid Valvular Disease

Tricuspid stenosis with or without insufficiency is very rare.[124] *Ebstein's disease*[59, 221, 17] is a congenital downward displacement of the tricuspid valve into the right ventricle. The tricuspid valve is usually competent and there are usually no clinical symptoms. However, premature beats and attacks of paroxysmal tachycardia are not infrequent. The electrocardiogram often discloses prolongation of the QRS.

Tricuspid atresia results from faulty development, but its exact pathogenesis is uncertain. Two forms are sometimes recognized. The more common is associated with auricular and ventricular septal defects.[140] The less common type, which presents a more favorable prognosis, is associated with transposition of the great vessels.[129, 57]

In the former cases the right ventricle is extremely small or rudimentary while the right atrium is greatly dilated. The left ventricle is hypertrophied. The pulmonary valve as well as the tricuspid may be atresic, since the right ventricle does not function.

If the interatrial septal defect is small, the heart functions as a triloculate heart (pseudo-triloculare-biatrium), blood passing from the right to the left atrium, thence to the left ventricle and aorta. From the left ventricle some blood reaches the pulmonary artery and lungs by way of the ventricular septal defect. If the ventricular septum is intact, blood is supplied to the lungs from the aorta through a patent ductus arteriosus. If the auricular septal defect is very large, both atria function as a single chamber and the heart as a biloculate chamber. Sometimes tricuspid atresia is associated with transposition of the aorta and pulmonary artery, which are so situated as to receive oxygenated and venous blood respectively despite their transposition. In this way cyanosis is avoided and the patient may have a normal life expectancy.

In the usual case, cyanosis appears very early and death occurs in infancy. There may be no murmur or a mesocardial systolic murmur which is heard all over the precordium.[33] In cases with a small auricular septal defect which offers resistance to the flow of blood from the right to the left atrium, blood is forced back to the inferior vena cava, giving rise to a presystolic liver pulsation.

In the anteroposterior view, roentgen ray examination reveals an enlarged globular heart with a sharp concavity in the region of the pulmonary conus, which is rudimentary. In the left anterior oblique view there is little or no shadow anteriorly where the right ventricle should be, while the shadow of the left ventricle is enlarged. The shadow of the great vessels is narrow and the pulmonic window is clear.

The electrocardiogram reveals left axis deviation. The P waves may be enlarged due to atrial hypertrophy.

The diagnosis of tricuspid atresia should be strongly suspected in a cyanotic patient with congenital heart disease if the left ventricle is enlarged and the electrocardiogram shows a left axis deviation.

Treatment. The cases of tricuspid atresia with rudimentary right ventricle and auricular septal defect as well as those of nonfunctioning right ventricle with auricular septal defect, pulmonary atresia and patent ductus are amenable to the Blalock-Taussig operation (p. 656).

Mitral Valvular Disease

Mitral stenosis is usually associated with an interatrial septal defect in so-called Lutembacher's syndrome (p. 644). There is a difference of opinion as to whether the mitral lesion is of congenital or rheumatic origin but in my experience at least some cases are unequivocally congenital.

Mitral atresia is associated with hypoplasia of the left cardiac chambers and aortic atresia, and is combined with other defects, such as complete absence of the interventricular septum (cor biatrium triloculare),[208] ventricular and atrial septal defects, patent ductus arteriosus[116] and with transposition of the great vessels.

Transposition of the Great Vessels

The most important clinical form of transposition of the great vessels is that associated with a ventricular septal defect and pulmonary stenosis. This has been discussed in the section on the tetralogy of Fallot. That section also considers the embryology.[29] Various forms of transposition have been noted. The aorta may override both ventricles which communicate by a septal defect (reitende or riding aorta) known also as type I of Spitzer.[98] Both vessels may

arise from a single ventricle, usually the right (simple or partial transposition or dextroposition of the aorta), known also as type II of Spitzer. Complete transposition or Spitzer's type III refers to cases in which the aorta arises from the right and the pulmonary artery from the left ventricle. Sometimes the aorta and pulmonary artery arise from the proper ventricles but are reversed in their relation to each other (corrected transposition).

The first three types are all associated with a large admixture of venous and arterial blood sufficient to cause cyanosis. In type III (complete transposition), life is impossible without an associated lesion, such as a patent ductus and/or an auricular or ventricular septal defect, which permits crossing of the systemic and pulmonary circulations.[107, 133] For otherwise the venous blood from the right ventricle flows through the aorta and systemic circulation and back to the right atrium without traversing the lungs.

The clinical picture of transposition of the great vessels has been noted by Kato,[107] and by Taussig.[198] Cyanosis is a constant feature but there are no characteristic physical signs, since the latter are determined essentially by the associated anomalies. The diagnosis can often be made, however, by the combination of cyanosis with distinctive roentgenologic findings. According to Taussig[198] the cases of complete transposition of the great vessels are characterized by: (1) persistent cyanosis, (2) cardiac enlargement, especially of the right ventricle, (3) a narrow aortic shadow in the anteroposterior roentgenogram, and (4) an increase in the width of the shadow of the great vessels in the left anterior oblique position. This widening is due to the fact that the pulmonary artery lies hidden behind the aorta and comes to view in the oblique position. For the same reason, the pulmonary salient appears concave in the anteroposterior view. Transposition of the great vessels may be demonstrated by intravenous cardiography, using either thorotrast or diodrast. Castellanos and his co-workers,[37] using the former, found that the solution injected into the jugular vein passed directly from the right ventricle into the aorta. Complete transposition may be differentiated by means of x-ray films from tetralogy of Fallot, which it resembles closely. In the former there are exaggerated vascular markings extending almost to the periphery of the lung fields.[198]

When transposition of the great vessels is associated with aortic isthmus atresia (aorta beyond left subclavian up to the insertion of the ductus), the ductus arteriosus is patent and supplies blood to the distal descending aorta and therefore to the lower extremities. In such cases the head and upper extremities are more cyanotic than the lower. In cases of isthmus atresia without transposition of the great vessels, cyanosis appears only in the lower extremities.

The Blalock procedure is not suitable for treatment of complete transposition of the aorta and pulmonary artery. However, Hanlon and Blalock[96a] have shown experimentally that the circulation may be improved by anastomosis of the pulmonary veins to the superior vena cava.

ANOMALIES OF THE CORONARY ARTERIES

The most frequent coronary anomalies are the presence of more than two coronary ostia, an unusual site of origin of some of the coronary arteries or an abnormal course. The right coronary or the left coronary artery may be absent, branches of the single coronary artery supplying all parts of the heart.[117, 170] In 3 of the 9 cases reported by Roberts and Loube[170] there was occlusion of the single coronary artery with ensuing myocardial infarction. Of grave

clinical significance is the origin of the right or more often the left coronary artery from the pulmonary artery, so that it carries venous blood to the heart.[187, 108] When the left coronary artery is concerned, necrosis and fibrosis of the left ventricle are consequences of the myocardial anoxia. Marked dilatation of the heart is common, and death usually occurs in infancy, though the patient occasionally reaches adult life. There may be an anginal syndrome and electrocardiographic evidence of myocardial disease. The association of distress on nursing, cardiac enlargement without murmurs and a coronary type of T wave in the electrocardiogram should suggest the diagnosis. Eidlow and Mackenzie[60] made the correct diagnosis during life in a three months old infant on the basis of paroxysms of cardiac pain associated with sweating, pallor, cyanosis and dyspnea, great enlargement of the heart, and inversion of T_1 and T_2 and deep Q_1 in the electrocardiogram. In most of the cases in which the *right* coronary artery arose from the pulmonary artery there was no myocardial fibrosis, cardiac enlargement or serious clinical consequences.[182, 108]

The *fetal left superior vena cava may persist* and replace the coronary sinus. This is of no clinical significance.

ANOMALIES OF THE GREAT VEINS

The *anomalous entrance of all four pulmonary veins into the right atrium* is a serious condition in which death from heart failure occurs usually before six months of age. Life is possible only when the foramen ovale is patent. The characteristic features are advanced enlargement of the right atrium and right ventricle, absence of cyanosis until the terminal collapse, frequent pulmonary congestion due to excessive pulmonary blood flow, compression of the left lower lobe of the lung by the large right ventricle and frequent paroxysmal tachycardia. Cardiac catheterization discloses that the oxygen content and saturation of right atrial blood is very high and identical with the oxygen content of arterial blood.

The commonest defect of the great veins is the persistence of the left superior vena cava which empties into the right atrium by way of the coronary sinus. This is of no significance. However, occasionally the pulmonary veins empty into the persistent left superior vena cava and produce the same clinical picture as when they empty into the right atrium.[136]

PERICARDIAL DEFECTS

The parietal pericardium may be completely absent, or only partially incomplete, usually in the region of the pulmonary artery.[83] In cases of ectopia cordis, the parietal pericardium may be missing or intact. When the pericardium is missing, the fetus is usually nonviable; when it is intact, the outlook may be favorable. The characteristic feature in the absence of the parietal pericardium is the complete mobility of the heart, both on respiration and change of position of the body. This may be demonstrable on physical and roentgenoscopic examination. There may be no symptoms, or thoracic pain, circulatory disturbance and even death may result from kinking of the great vessels due to cardiac mobility. An even more common complication, in cases with partial or complete absence of the parietal pericardium, is the frequency of pneumonia, pleurisy with effusion, empyema or pericarditis due to the juxtaposition of the heart and left lung without an intervening pericardial sac.[193]

More rarely there is a diverticulum of the pericardium or failure of attach-

ment of the parietal pericardium. These are of no clinical significance unless the orifice of the diverticulum becomes occluded and the consequent distention of the diverticulum interferes with cardiac contraction.

Anomalous Bands, Chordae, and Papillary Muscles

Occasionally (2 to 3 per cent of hearts), there is a network of thread-like strands or a fenestrated membrane in the right atrium continuous with the eustachian or thebesian valves.[39, 219] This is known as a Chiari network. It may extend across the atrial cavity and be attached to the upper part of the interauricular septum. It is believed to represent a residuum or persistence of the valvula venosa dextra together with the septum spurium. It is usually an incidental postmortem finding, but it may be clinically significant in two ways. First, it may act as a favorable site for the formation of thrombi with consequent pulmonary embolism.[149a] Second, it rarely gives rise to an unusual continuous or systolic murmur which may resemble a venous hum or be confused with the bruit de Roger.[216]

Anomalous chordae may extend across the left ventricular cavity from an individual papillary muscle to an attachment high up on a mitral cusp or to the left auricle. They may cause confusing adventitious sounds or murmurs. Papillary muscles may have unusual sites or attachments, e. g., to a pulmonary valve.[41]

The left atrium may be subdivided into two chambers when the septum primum is deflected to the left leaving a cavity between it and the septum secundum. Cardiac failure may supervene.

DIAGNOSIS OF CONGENITAL HEART DISEASE

The diagnosis usually involves the recognition of the congenital nature of a cardiac lesion and the determination of the site and character of the lesion itself. The presence of an organic cardiac murmur, of cardiac enlargement, or of dyspnea or cyanosis and clubbing, without bronchopulmonary disease or brain injury, beginning in infancy or early childhood should suggest congenital heart disease. Rheumatic heart disease is very uncommon before the age of five and rare before the age of three. If the patient is first seen in late childhood or after puberty, the congenital nature of the lesion may be suspected from the history of a cardiac murmur or other evidence of heart disease since birth or early childhood. A harsh systolic murmur and thrill denote congenital heart disease if they are discovered before the age of twenty. The absence of a history of rheumatic fever is confirmatory evidence.

An analysis of the signs and symptoms usually permits a clinical diagnosis of the common forms of congenital heart disease. Certain characteristic manifestations reveal the congenital origin of specific cardiac anomalies even when there is no history of a lesion since birth.

Cyanosis and Cardiac Enlargement in Infancy and Later. Cardiac enlargement and cyanosis in infancy without an associated murmur suggest the diagnosis of complete transposition of the great vessels. Atresia of the aortic isthmus may produce a similar picture but the cyanosis is limited to the lower extremities if there is no transposition, while cyanosis is more intense in the upper half of the body if transposition and isthmus atresia are associated. Nonfunctioning right ventricle is distinguished by left axis deviation and left ventricular enlargement.

If cardiac enlargement, cyanosis and a murmur are present in infancy, the diagnostic possibilities are very numerous and require systematic study of the location of the murmurs, roentgenoscopy, angiocardiography, etc.

After the first three years of life, cardiac enlargement, murmur and cyanosis are usually due to tetralogy of Fallot, but less common conditions need to be differentiated (p. 655).

Murmurs. In early infancy there may be a generalized systolic murmur which only later assumes its characteristic quality and site of maximum intensity. A rough, loud murmur with maximum intensity in the second left interspace near the sternum may be due to a patent ductus arteriosus, pulmonic stenosis or the tetralogy of Fallot. Occasionally its maximum intensity is one interspace lower. The murmur of a patent ductus arteriosus is usually a pathognomonic machinery-like murmur extending through systole and diastole. The second pulmonic sound is accentuated. In aortic septal defect the machinery murmur is heard maximally over the lower sternum or in the fourth left interspace. The murmur of pulmonary stenosis is purely systolic and the second pulmonic sound is weak or absent.

A loud systolic murmur, with maximum intensity in the third or fourth interspace to the left of the sternum, should suggest an interventricular septal defect (maladie de Roger). The murmur becomes distinctly weaker toward the clavicle or apex, but is often transmitted to the left scapular region. The atrial septal defect is associated with a variable murmur which may also be located in the third left interspace near the sternum. If there is an associated mitral stenosis, a presystolic apical murmur may be audible. Systolic murmurs in the interscapular regions, axilla or along the sternum may be found in cases of adult coarctation of the aorta with well developed collateral circulation. A harsh systolic murmur and thrill, loudest in the second right interspace, suggests subaortic stenosis.

Thrills are not diagnostic. They do help to confirm the organic nature of a systolic murmur. Furthermore, in acquired heart disease they occur almost exclusively in systole over the aorta (aortic stenosis) or in diastole over the apex (mitral stenosis). Thrills in the second, third or fourth left interspace near the sternum almost invariably indicate the presence of congenital heart disease, except when there is a sudden perforation or tear of a cardiac structure.

Roentgenologic Signs. Roentgen ray examination of the chest is invaluable in the diagnosis of many of the common congenital cardiac lesions, but only a few of these are associated with a pathognomonic cardiac contour. But with other lesions the roentgen ray configuration of the heart is either fairly characteristic or is of great diagnostic help when interpreted in association with the clinical history and physical signs. Fluoroscopy, oblique views and examination after a barium swallow are essential in addition to a conventional roentgenogram of the chest.

The diagnosis of dextrocardia can be made from the roentgen ray examination alone. The bulk of the cardiac shadow is to the right of the midline. The right leaf of the diaphragm is lower than the left. In cases of true dextrocardia the electrocardiogram will prove the diagnosis.

Adult coarctation of the aorta is often associated with smooth notching of the lower borders of the posterior ribs and occasionally with a localized defect

in the descending arch of the aorta when viewed in the left anterior oblique position. Hypertension, weak or absent femoral pulsation and evidence of collateral circulation in the chest wall are also present in most cases.

Persistent *right-sided aortic arch* presents distinctive features: a pulsation shadow of the right aortic arch to the right of the sternum, small or absent left aortic knob, displacement of trachea and especially of the barium-filled esophagus to the left and forward.

Fairly characteristic cardiac shadows are encountered in cases of the tetralogy of Fallot, atrial septal defect with mitral stenosis, tricuspid atresia with hypoplasia of the right ventricle, and cor triloculare biatrium. The *tetralogy of Fallot* may be associated with a coeur en sabot, the lower left contour being blunt like a sheep's nose, the right ventricle being massive and protruding forward in lateral or oblique views, while the pulmonary artery is small or not enlarged. The association of cyanosis, clubbing and marked right axis deviation in the electrocardiogram, in addition to the systolic murmur mentioned above, confirms the diagnosis.

In cases of large *atrial septal defect, usually associated with mitral stenosis,* there is a large globular heart with large pulmonary artery and branches, small aortic knob, and exaggerated pulsation of the pulmonary artery branches. Confirmation is provided by intracardiac catheterization studies.

Tricuspid atresia with hypoplasia of the right ventricle is denoted by left ventricular enlargement, and considerable diminution of the right ventricular shadow. The diagnosis is confirmed by the association with cyanosis and left axis deviation on the electrocardiogram.

Cor triloculare biatrium is suggested by a heart of water bottle shape in an infant or young child with cyanosis, and sometimes isolated dextrocardia.

Other abnormal cardiac silhouettes are not characteristic, but aid in confirming a diagnosis made on other grounds or in suggesting the presence of cardiac disease. Generalized cardiac enlargement without murmurs may be due to a bilocular or trilocular heart, origin of a coronary artery from the pulmonary artery, von Gierke's disease or cases of so-called idiopathic hypertrophy. Prominence of the pulmonary artery may be due to patency of the ductus arteriosus, pulmonary insufficiency, a large ventricular septal defect, tetralogy of Eisenmenger or acquired heart disease. In cases of patent ductus, the heart usually is not enlarged or the left ventricle is enlarged, and pulmonary congestion is noted. In cases of pulmonary valvular stenosis the pulmonary artery may be dilated, but with infundibular stenosis the pulmonary salient is concave. Hypertrophy of the left ventricle occurs with aortic or subaortic stenosis, patent ductus arteriosus, coarctation of the aorta, tricuspid atresia and nonfunctioning right ventricle and sometimes with pulmonary atresia. The mediastinal vessels are narrow in cases of pulmonary or aortic atresia or transposition of the great vessels. But in cases of the latter, the shadow becomes widened in the oblique view. Among the common congenital anomalies, a small foramen ovale or interventricular septal defect usually is not associated with significant roentgenologic abnormalities.

Electrocardiogram. The electrocardiogram is characteristic in cases of true dextrocardia (p. 674). The occurrence of heart block suggests a ventricular septal defect. In other cases, the electrocardiogram helps more by exclusion than in a positive way. Thus most congenital lesions of the heart, especially

interatrial septal defect with mitral stenosis, pulmonary stenosis or insufficiency and the tetralogy of Fallot, are associated with right axis deviation. Patent ductus is excluded by the presence of definite right axis deviation. The presence of left axis deviation excludes these conditions. Left axis deviation in a cyanotic patient suggests either tricuspid or pulmonary atresia. Left axis deviation without cyanosis suggests aortic or subaortic stenosis and coarctation of the aorta. Occasionally patent ductus is associated with left axis deviation.

Angiocardiography. Angiocardiography has become one of the most valuable technics in the diagnosis of congenital heart disease. It reveals with more certainty than the conventional roentgenogram the specific chambers or vessels affected by enlargement or malposition. It discloses the sequence of the circulation. It differentiates between aneurysms and thoracic tumors unrelated to the cardiovascular system. When surgical correction of a cardiac anomaly is contemplated, angiocardiography serves to confirm the preoperative diagnosis, discloses or excludes associated anomalies and reveals the size, position and configuration of structures important to the surgeon.

The technic has been described by Robb and Steinberg[168] and by Sussman and Grishman.[194] A 70 per cent solution of diodrast (35 to 40 cc. in adults; 8 to 25 cc. in children) is employed for contrast visualization. The patient is placed in proper position, with the arm to be injected raised above his head, in front of the recording roentgen ray apparatus. A #12 needle with a stopcock unit (B-D) is inserted into an antecubital vein, exposed by a small incision. During a deep inspiration (after forcible expiration), the solution is injected *as rapidly as possible* and successive films are made with the aid of multiple cassettes which automatically slide into position while the patient holds his breath.* The exposures are begun as the last 5 to 10 cc. is injected and completed in about 8 to 10 seconds, depending on the patient's circulation time. A small plastic tubing technic has recently been recommended for catheterization of the right and left heart.[69a]

Angiocardiography permits a precise diagnosis of dextrocardia, right aortic arch and coarctation of the aorta, stenosis of the pulmonary or left subclavian artery, dilatation of the pulmonary artery, by clear visualization of the position, size and configuration of the structures concerned. Right-to-left shunts in the tetralogy of Fallot and Eisenmenger are usually clearly disclosed. In patent ductus arteriosus, a distinctive aortic bulge is usually observed at the site of entrance of the ductus.

Hypertension in a young person should always suggest the possibility of adult coarctation of the aorta. A blood pressure which is significantly less in the lower than in the upper extremities, weakness or absence of the femoral pulse, evidence of a collateral circulation in the chest wall, and notching of the lower borders of the ribs, observed roentgenoscopically, prove the diagnosis. The possibility of congenital heart disease should also be considered in cases of young persons with cerebrovascular accidents, in subjects with congenital anomalies such as mongolism and in patients with subacute bacterial endocarditis.

Circulation Time Studies. The presence of a venous-arterial (right-to-left) shunt may be demonstrated by the administration of ether and saccharin as in the tests for determining the circulation time (p. 139). When such a shunt exists, the ether reaches the systemic capillaries and causes distinct unpleasant pares-

* The method has been improved by use of a rapidograph which adapts the Fairchild aerial camera to roll film 9½ inches wide and permits exposures every half second. (Scott, W. G., et al.: Exhibit A.M.A., June, 1949.)

thesias of the skin of the face and subsequently of the extremities.[15] This has been observed particularly in cases of the tetralogy of Fallot but it probably also occurs terminally in cases of auricular or ventricular septal defects or patent ductus arteriosus when the usual left-to-right shunt is reversed. It also occurs in trilocular or bilocular hearts or in cases with extensive septal defects which are practically tantamount to bilocular hearts, in which there is a fairly free mixing of arterial and venous blood, even when the major current is in one direction. In children, as little as 1 or 2 minims of ether may produce the effect.

At the same time, if the shunt is considerable, the usual dose of saccharin, being rather more than the minimum necessary for an end point, will in cases of right-to-left shunt pass directly to the systemic circulation and the capillaries of the tongue, without traversing the pulmonary circulation. In such cases, the saccharin time instead of being approximately twice the ether time is equal to the ether time.[15, 135] But with right-to-left shunts which are less than 50 per cent, the major portion of the saccharin will traverse the pulmonary circulation and the amount shunted directly to the systemic circulation is inadequate to produce the early end point. In such cases ether paresthesias may be obtained but the saccharin time, as normally, is about twice the ether time. By determining the minimal dose giving a saccharin end point, and then increasing the dose until a sharp reduction in circulation time was obtained, Prinzmetal[161] calculated the approximate size of the shunt.

Cardiovascular Catheterization. The method of intracardiac catheterization has been described by Cournand and Ranges[43] and its use in congenital heart disease by Sosman[188] and by Dexter.[50]

Technic. Under local anesthesia, a 9 French radiopaque catheter, 100 cm. long, curved near its end, and with a hole at its tip, is introduced aseptically into either median basilic vein, with the aid of a small incision. The catheter is advanced rapidly under fluoroscopic control. With experience the catheter can be rotated as it advances and can be made to enter successively the superior vena cava, right atrium and ventricle and vena cava. In the right atrium the coronary sinus may be entered, or if there is an atrial septal defect, the left atrium and pulmonary vein. To prevent coagulation, a slow continuous intravenous drip of normal saline, containing 1 mg. per 100 cc. of heparin, is maintained.

Blood samples are collected under oil from the various chambers and vessels and analyzed for oxygen capacity and content. Spot films serve to localize the exact site of the catheter at the time samples are taken. Pressures in the various chambers or vessels can be measured with the aid of a Hamilton or strain gauge manometer connected to the external end of the catheter. To aid interpretation of blood oxygen findings, an arterial blood sample is drawn simultaneously and its oxygen content determined. Oxygen consumption is measured by the Benedict-Roth spirometer as this value is needed in the Fick formula to determine cardiac output and pulmonary blood flow. When the catheter is withdrawn angiocardiograms can be made by injecting diodrast through a needle in the same vein.

Diagnostic Applications. In cases of interatrial septal defect the right atrial blood oxygen content significantly exceeds (by 2 volumes per 100 cc. or more) that of the superior vena cava or the average of both venae cavae. The

catheter may pass through the septal defect. When the pulmonary veins empty into the right atrium the right atrial blood oxygen is not only high but equals the oxygen content of a peripheral artery.

In cases of interventricular septal defect the right ventricular blood oxygen content significantly exceeds (by 1 vol. per 100 cc. or more) that of the right atrium. Similar findings are noted in cases of tetralogy of Fallot and Eisenmenger, but with tetralogy of Fallot the pulmonary arterial pressure is lower than that of the right ventricle.

In cases of patent ductus arteriosus the pulmonary arterial oxygen exceeds that of the right ventricle by at least 0.5 volumes per 100 cc.

The volume of the shunt can be calculated by determining the pulmonary blood flow and peripheral blood flow and subtracting. Pulmonary blood flow by the Fick formula equals oxygen consumption divided by oxygen taken up in lungs (systemic arterial oxygen content — pulmonary arterial oxygen content). Peripheral blood flow equals oxygen consumption divided by oxygen loss in the periphery (systemic arterial oxygen content — right ventricular oxygen content). Determination of the pulmonary blood flow is of value in evaluating the indications for the Blalock-Taussig operation which is designed to increase a subnormal pulmonary blood flow. If the pulmonary blood flow is normal or increased, the procedure is not indicated.

Oximetry and Exercise. The determination of oxygen consumption per liter of ventilation and of arterial oxygen saturation following exercise and after breathing pure oxygen is also of diagnostic aid.[19] (See p. 651.)

PROGNOSIS IN CONGENITAL HEART DISEASE

More than half of the subjects with congenital cardiac anomalies die in the first two years of life. About 75 per cent of the deaths in Leech's[120] series and 73 per cent in the series of Ash and Harshaw[6] occurred in the first year of life. In the latter series, 70 per cent of those who died and only 20 per cent of those who were still alive had cyanosis. In the first year of life, the death rate was twice as high among cyanotic infants with congenital heart disease as among those who were free from cyanosis. Thus in general the association of cyanosis implies a less favorable prognosis than freedom from this manifestation. After the age of two, the death rate drops sharply in patients with congenital heart disease without cyanosis.

Certain lesions may permit a relatively asymptomatic existence and fair or even normal life span. These include a patent foramen ovale, an uncomplicated interventricular septal defect, patent ductus arteriosus and a subaortic stenosis. Much depends on the size of the lesion and the consequent size of the shunt in the first three. The prognosis must often be guarded, not because of the lesion itself, but because of the frequency of associated rheumatic cardiovalvular disease and especially of subacute bacterial endocarditis. These occur particularly in cases of patent ductus arteriosus, interventricular septal defects and coarctation of the aorta. Death may occur suddenly in patients who are relatively asymptomatic, especially in connection with coarctation of the aorta.

The attainment of adult life, the absence of cyanosis, minimal or no cardiac enlargement, few or no symptoms of cardiac strain are favorable elements in regard to prognosis. Each case must be individually evaluated with regard to these factors. But at best the danger of complications is so great that prognosis is always beset by uncertainty.

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31

RHEUMATIC FEVER

Etiology, Pathogenesis and Pathology

GENERAL CONSIDERATIONS

Nomenclature. The term, *rheumatic fever,* a heritage from a period when the cardiac involvement was not recognized, exaggerates the more obvious joint symptoms. *Acute* rheumatic fever is objectionable because the disease is essentially not an acute but a chronic one; *rheumatic* is a nonspecific term for various types of muscle and joint pains; and *fever* is commonly absent. It seems unnecessary to criticize individually the various substitutes that have been offered, including acute articular rheumatism, the rheumatic state,[13] acute rheumatism, specific infectious rheumatism,[47] acute rheumatic polyarthritis, rheumatic granulomatosis[34] and Bouillaud's disease. The essential difficulty in nomenclature is due to our ignorance of the specific causative agent or etiologic mechanism determining the disease. Until such etiology is ascertained, it is best to employ terms sanctioned by usage and least susceptible of misunderstanding. In the following discussion, rheumatic fever is used to denote the general disease and rheumatic heart disease its cardiac manifestations.

Cardiac disease is the most serious manifestation of rheumatic fever. It is erroneous to consider cardiac involvement merely a complication of this disease, because it occurs almost as often as any other symptom, the heart rarely escaping damage in the chronic life history of rheumatic fever. The two are so intimately associated that they must be considered together. Since there is no specific reliable test for rheumatic infection, only a complete understanding of all the manifestations of rheumatic fever will lead to a thorough recognition of the presence of rheumatic heart disease. Even when cardiac involvement is absent in the early stages, the physician's diagnosis of rheumatic fever is a warning of potential cardiac disease, since the victim of rheumatic fever is a favored candidate for acute recurrences which may spare the heart at first but rarely later. Of 100 consecutive cases of rheumatic fever seen by Coombs,[24] predominantly in children, 59 presented signs of carditis at their first visit and many of the others developed such signs later so that at least 75 per cent eventually manifested some cardiac lesion. Some series indicate an even higher incidence of cardiac involvement in rheumatic fever.[22] *Practically, the importance of rheumatic fever lies in the frequency and seriousness of its cardiac lesions.*

Incidence and Importance of Rheumatic Fever and Rheumatic Heart Disease. A host of statistical surveys attest to the relative frequency and importance of rheumatic fever and its cardiac disturbances. The data vary according to studies made in urban or rural communities, temperate, subtropical or tropical regions, seasons of the year, among school children or general population, civilians and military personnel, as well as with differences in diagnostic criteria and acumen.

Patients with rheumatic fever form 3 to 7 per cent of the total sick admitted to the large general hospitals of Europe and the United States.[103] Accurate determinations of the incidence of rheumatic fever and heart disease are impossible since the disease is not generally reportable and its diagnosis is frequently indefinite. In the Scandinavian countries where rheumatic fever is reportable, the incidence is between 1 and 3 per thousand. Estimates based on various statistical analyses indicate that there are about one million cases of rheumatic heart disease in the United States.[103, 86] Reports from the British Ministry of Health[3, 48] indicate that there are 25,000 fatal cases of rheumatic heart disease annually in England and Wales, that these form 40 per cent of all cardiac deaths and that in two thirds of these cases heart disease developed between the ages of five and fifteen.

The highest incidence of rheumatic fever and rheumatic heart disease is among children and adolescents. According to studies in the schools of several large cities, rheumatic heart disease was encountered in 2 to 4 per thousand children between the ages of six and nineteen.[62, 144] In New England and in London, the incidence is closer to 2 per cent. Keith[72] estimated that rheumatic heart disease occurs in 0.9 to 1.36 per cent of American, 0.1 to 2.08 per cent of British and 0.36 to 3.92 per cent of Canadian school children. The seriousness of rheumatic heart disease among young people is indicated by mortality statistics. In the age groups between 5 to 9, 10 to 14 and 15 to 19, rheumatic fever and heart disease ranks first as the cause of death, exceeding such diseases as tuberculosis and appendicitis as well as the combined mortality from all of the common contagious diseases. Between 20 and 24, rheumatic fever ranks second only to tuberculosis as a cause of death. Recent statistics indicate that there has been a progressive reduction in the mortality rate among young people aged 5 to 24 from rheumatic fever (1.6 per 100,000 in 1943) and from rheumatic heart disease (about 8 per 100,000 in 1943).[92, 62, 46] However, in the same age group deaths from rheumatic fever and heart disease relative to all fatalities have increased, because there has been a greater reduction in deaths from other causes than from rheumatic heart disease. The incidence of new cases of rheumatic fever in New York City appears to have diminished strikingly in the past five years. This may be related to the widespread use of the sulfonamides and antibiotics in nasopharyngeal and tonsillar infections.

Studies of the incidence of rheumatic heart disease and rheumatic fever among selective service applicants, drafted troops and military personnel also attest to the importance of this disease.[87, 89] Among the first two million American selectees between the ages of twenty-one to thirty-six in the second World War, about 100,000 were found to be unfit because of cardiovascular disease.[119] Reexamination by expert cardiologists of these disqualified individuals disclosed that at least 50 per cent suffered from rheumatic valvular defects.[79, 36] According to Barber[6] the incidence of rheumatic fever in the British Royal Air Force was 2 per 1000 while in the more limited group of boy entrants and apprentices

the incidence was 10.4 per 1000. Recent reports of the occurrence of rheumatic heart disease and especially of first or recurrent attacks of rheumatic fever in the U.S. Navy,[18, 85] Air Force,[65] and Army[8] during the second World War reemphasize previous data on the frequency and importance of this disease.

The incidence of rheumatic heart disease relative to other etiologic types of heart disease varies in different localities according to the relative frequency of rheumatic fever. In large cities of temperate zones such as New York, Boston and London, rheumatic heart disease represents between 25 and 35 per cent of all cardiac ailments. In these places it ranks slightly below (coronary) arteriosclerotic and hypertensive heart disease. Below the age of fifty it is the commonest type of organic cardiac ailment. However, in many southern regions of the United States and in other localities with a high incidence of syphilis, rheumatic heart disease is said to follow arteriosclerotic, hypertensive and syphilitic heart disease in that order.

Public Health Aspects. The frequency and importance of rheumatic fever and heart disease among school children, drafted troops, applicants for life insurance, and industrial workers emphasize the need for a public health program. With due allowance for statistical inadequacies, the available data teach the tragic lesson that in contrast with other major forms of heart disease, rheumatic heart disease maims its victim before adolescence, impairs his efficiency and earning power throughout adult life and usually destroys him in his prime. Many analogies with tuberculosis including the chronicity of rheumatic fever, social and economic predisposing factors, evidence of infectious etiology, as well as the greater mortality from rheumatic heart disease among young subjects, suggest the need for a public health program and the hope that such a program with respect to rheumatic fever, as with tuberculosis, will yield gratifying accomplishments. However, it is important to stress that any contemplated public health program for rheumatic fever is handicapped by our ignorance of its exact cause, and by the lack of some exact diagnostic test or specific treatment.

The need for a public health program and suggestions for such a program have been repeatedly presented.[129, 72, 103, 120, 70] London has developed a scheme for the treatment and supervision of juvenile rheumatism,[134, 4] making rheumatic fever a reportable disease and providing beds for the treatment of rheumatic fever patients at public expense. Special hospital units devoted exclusively to rheumatic fever have been built. Emphasis has been placed on the chronic, relapsing nature of the disease. Similar programs have been initiated in individual states in this country and a more concerted national effort in this direction has begun since the end of the war. The Children's Bureau of the Department of Labor and the American Heart Association have been most active.

It is important to have a central integrating agency which keeps a registry of rheumatic fever patients and which coordinates the work of various interested public and private agencies. Rheumatic fever should be a reportable disease. Expert clinical and laboratory facilities should be made available for aid to the physician in the diagnosis, treatment and follow-up of patients. Case-finding methods should be improved and used more widely, especially in schools and among siblings of known rheumatic fever patients. Nursing, hospital and social service facilities need to be enhanced. Hospital facilities should take cognizance of rheumatic fever as a chronic disease as well as of its acute

and subacute manifestations. Rehabilitation programs should be developed and vocational guidance should be made available to rheumatic patients after convalescence. Cooperation of employers should be obtained to aid in the placement of rheumatic patients in industry. Research facilities need to be fostered and augmented with respect to epidemiology, etiology, clinical and laboratory features. Educational programs should be designed for physicians, nurses, welfare workers and the lay public.

DEFINITION AND CRITERIA

Rheumatic fever is a chronic inflammatory disease generally punctuated by recurrent acute episodes. Its exact cause is unknown. It is probably infectious. However, there is disagreement as to whether it is a *specific* infectious disease. The strongest evidence for specificity, as presented by pathologists, is the Aschoff body, a granulomatous lesion analogous to the tubercle of tuberculosis or the gumma of syphilis. There are additional pathologic lesions in rheumatic fever whose structure and distribution are almost specific for the disease. Certain clinical features (e.g., mitral stenosis) are likewise of a specific or almost specific nature.

There is no special diagnostic laboratory test for rheumatic fever. Fairly rigid criteria are available for diagnosis post mortem, especially when Aschoff bodies are present. But as will be indicated in the section on Pathology, the diagnosis can generally be made even in the absence of these bodies. The clinical diagnosis is dependent on less rigid criteria and requires a general consideration of the presence of numerous, often seemingly unrelated, clinical features including chorea, cutaneous lesions, hemorrhagic and pleuropulmonary as well as cardiac and arthritic symptoms. Some of these, like erythema annulare, subcutaneous nodules, chorea or mitral stenosis, occurring in children or young individuals, are practically pathognomonic of rheumatic heart disease.

ETIOLOGY AND PATHOGENESIS

Infectious Nature of Rheumatic Fever

Belief in the infectious nature of rheumatic fever is based on (1) the outbreak of epidemics, (2) its occurrence with or after infectious diseases, (3) a comparatively high familial association, (4) the similarity of its climatic distribution and seasonal occurrence to that of other well known infections, and (5) various clinical, pathologic, bacteriologic and immunologic considerations (infra).

1. On the basis of numerous hospital statistics, Newsholme[99] pointed out that in certain years the incidence of rheumatic fever reached epidemic proportions. Various epidemics of the disease were observed in army, navy and air force barracks.[2, 44, 17, 18, 49, 65] Grenet[51] reported an epidemic in a regiment located in a certain sector. When this regiment was removed to a distant area, additional cases broke out among them. On the other hand a new regiment which occupied the original, affected area was unaffected. These observations tended to indicate that the disease was spread from man to man independent of environment. Epidemics of rheumatic fever have also been reported in various schools, and in connection with the establishment of hospitals or convalescent homes for rheumatic cardiacs.

2. A remarkable feature noted in these and other reports was the occurrence of the epidemics following outbreaks of acute tonsillitis, pharyngitis or other respiratory infections, and after scarlet fever (p. 697). Of course it is generally impossible to be certain that these rheumatic outbreaks are truly epidemics and not merely simultaneous reactivations of the rheumatic process in rheumatic individuals by incidental respiratory infections.

3. A number of writers have noted a relatively high incidence of rheumatic fever occurring in more than one member of a family.[122, 67] St. Lawrence[122] observed that the incidence of familial rheumatic fever was identical with that of familial tuberculosis. He interpreted this as indicating that rheumatic fever, like tuberculosis, was of infectious nature. Paul and Salinger's[105] observations on the spread of rheumatic fever through families could also be interpreted to indicate the infectious nature of the disease, for both the initiation of the disease and periods of recurrent activity occurred simultaneously in different members of a given family.

4. Rheumatic fever, like several other infectious diseases, occurs rarely or infrequently in subtropical or tropical regions and in the warm and dry seasons of the year (p. 703). In this respect it particularly resembles the streptococcal infections. Years in which the incidence of rheumatic fever is high are associated also with a high incidence of these infections. Dudley[30] has noted a similarity in incidence of rheumatic fever with tonsillitis and with pneumococcus pneumonitis. Glover[44] observed that the incidence and spread of rheumatic fever was similar to that of cerebrospinal fever and concluded that like the latter it was disseminated by droplet infection.

5. Clinically, rheumatic fever resembles other infectious diseases in the occurrence of fever, sweats, leukocytosis, increased rate of sedimentation of erythrocytes, skin lesions, inflammatory pulmonary complications, etc. Pathologists generally have accepted an infectious etiology of rheumatic fever because of the analogy of the specific Aschoff body with the specific granuloma in other infectious diseases, because of the exudative and productive inflammatory lesions and because of the contiguous spread of the disease in the involved organs. The bacteriologic and immunologic evidence for the infectious nature of rheumatic fever is that which will be shortly presented favoring the specific etiology of various bacterial agents.

Specific Cause

No specific microorganism has been established as the cause of rheumatic fever. Most of the evidence concerning a causative agent has related to streptococci. But several other organisms have been invoked as the specific cause, including the tubercle bacillus, spirochetes and filterable viruses. The theories as to causation of rheumatic fever can be considered as (1) streptococcal, (2) allergic, (3) nonstreptococcal.

1. Streptococci as the Cause of Rheumatic Fever. The streptococcal theory has been intended by some investigators to indicate that rheumatic fever is due to a specific variety of streptococcus and by others to the whole group of streptococci. Various nonhemolytic, gamma types of streptococci have been proposed as the specific cause of rheumatic fever by Poynton and Paine[108] and others without adequate evidence or confirmation. Clawson[16] presented bacteriologic, experimental and other evidence favoring the Streptococcus viridans as the causative organism, but this hypothesis has been generally rejected. The

bulk of recent studies has incriminated the hemolytic streptococcus as an important factor in the development of initial and subsequent attacks of rheumatic fever.

Etiologic Importance of the Hemolytic Streptococcus. The etiologic importance of the hemolytic streptococcus is based on clinical, epidemiologic, bacteriologic and immunologic observations:

(1) *The occurrence of sore throat or tonsillitis just prior to an attack of rheumatic fever* is a common clinical observation. The frequency with which reported epidemics of rheumatic fever were preceded by epidemics of pharyngitis or tonsillitis, occurring one to three weeks earlier, has been mentioned. Schlesinger[123] in England and Coburn[18] in this country disclosed that the preceding pharyngeal infections were almost exclusively due to the hemolytic streptococcus. Family outbreaks of hemolytic streptococcal infections (Lancefield's type A) are followed in some members of the family by suppurative lesions such as otitis, in others by rheumatic fever.[103] A community outbreak of a milk-borne epidemic of streptococcus sore throat was followed two weeks later by many cases of rheumatic fever.[84] Epidemics of pharyngitis and tonsillitis in crowded populations of boarding schools have similarly been followed by rheumatic fever.[44, 29] Among naval recruits, crowded together in various stations during the last war, cases of rheumatic fever appeared within a few weeks after hemolytic streptococcal infections hit their peak.[87, 109]

(2) *The association of rheumatic fever with scarlet fever* was particularly noted by Cheadle[13] and others. Since scarlet fever is due to an erythrogenic strain of hemolytic streptococcus, and since typical clinical features[143, 127] and pathologic evidence[33, 40] of rheumatic fever and rheumatic heart disease are not infrequently observed one to three weeks after scarlet fever, this association may be interpreted to support the etiologic relationship of hemolytic streptococci to rheumatic fever.

(3) *Recurrences of rheumatic fever and carditis* always appear a few weeks after an hemolytic streptococcal oropharyngeal infection. In most of the reported epidemics of rheumatic fever, not only the initial attacks but also recrudescences followed infections with streptococcus A. In a high percentage of cases of rheumatic fever among naval recruits in the last war, a careful history and examination disclosed that the patient had previously experienced rheumatic fever and that the present attack represented a recrudescence following an hemolytic streptococcal infection. Among carefully studied small rheumatic populations in rheumatic cardiac convalescent homes, recurrences of rheumatic fever almost never appear except after an hemolytic streptococcal infection.

These observations do not signify that all cases of tonsillitis, scarlet fever or other hemolytic streptococcal infections are followed by an attack of rheumatic fever, even if the patient has already suffered a previous attack. Such streptococcal infections in normal children, adolescents or young adults are probably followed by rheumatic fever in 3 to 5 per cent of cases. Among subjects with previous rheumatic fever, a recurrence may be activated by streptococcus A infection in as many as 25 per cent or more. However, many of the forty or more strains composing Group A hemolytic streptococci may differ fundamentally in virulence and particularly in their ability to precipitate or activate rheumatic fever. Thus in the same group of rheumatic children one epidemic of streptococcus A infection induced a recurrence of rheumatic fever

in 50 per cent of the children, while two subsequent streptococcus A epidemic infections caused very few or no cases.[75] In some instances in which attacks of rheumatic fever are not preceded by overt respiratory infections, careful clinical observation may disclose mild pharyngitis or tonsillitis while nasal and pharyngeal cultures disclose the presence of hemolytic streptococci.

(4) *Hemolytic streptococcal infections and rheumatic fever are similar in their geographic, climatic and seasonal incidence.* Seegal et al.[126] pointed out that scarlet fever, like rheumatic fever, becomes less frequent as one travels from northern to southern United States and that hemolytic streptococci are found in throat flora less commonly in the subtropical and tropical islands of the West Indies than in the northern half of the United States. Farquhar and Paul[35] noted a similarity in the seasonal incidence of hospital admissions in New Haven between that of rheumatic fever and that of scarlet fever, acute tonsillitis and erysipelas. Coburn[17] noted that patients with active rheumatic fever in New York had hemolytic streptococci in their throats. When the patients were removed to Puerto Rico, the hemolytic streptococci disappeared from their throats and the disease became inactive.

(5) *Skin tests with derivatives of hemolytic streptococci* (nucleoprotein) have been reported as giving a higher incidence of positive reactions in patients with rheumatic fever and in those with hemolytic streptococcal infections than in nonrheumatic patients and in patients with nonstreptococcal infections.[17, 96] However, it is improbable that the skin sensitivity of rheumatic fever patients is a specific reaction to the hemolytic streptococcus or that the skin reactions elicited by this organism are obtained specifically in rheumatic fever and hemolytic streptococcal infections.[28]

(6) *Streptococcus hemolyticus antibodies.*[94] ANTISTREPTOLYSIN. Todd[137] reported the presence of an antigen termed *streptolysin* or *streptohemolysin* in the broth of hemolytic streptococcus cultures, which is hemolytic for the erythrocytes of rabbits. Two varieties have been described: streptolysin O (oxygen labile) and streptolysin S (oxygen stable).[63] The sera from horses which had been immunized with Streptococcus hemolyticus and the sera of humans convalescing from Streptococcus hemolyticus respiratory infections, including scarlet fever, were found to contain an antibody termed *antistreptolysin* (or antihemostreptolysin) which neutralized streptohemolysin and prevented its hemolytic action. It has also been found that about 90 per cent of patients suffering from acute rheumatic fever have abnormal quantities of antistreptolysin O in their serum.[138, 19] This finding has been interpreted to indicate a close relation between hemolytic streptococcal infections and rheumatic fever. The development of nonsuppurative complications, especially rheumatic fever, has been related to excessive antibody formation, of which the elevated antistreptolysin found in the gamma globulin fraction is one example.[111] The absence of antistreptolysin in some cases of hemolytic streptococcal infection or of rheumatic fever may be due to the failure of some of these streptococcal A strains to elaborate streptolysin O. The serum antistreptolysin S content of patients with acute rheumatic fever is lower than in patients with streptococcus A infections not followed by rheumatic fever.[139]

ANTIFIBRINOLYSIN. Broth cultures of hemolytic streptococci rapidly liquefy the fibrin clot of human plasma[136] due to the production by these bacteria of a serum zymogen (plasminogen) activator termed fibrinolysin (or streptokinase).[15] The streptokinase activates plasminogen to form plasmin, an active

proteinase which dissolves fibrin clot. Both in the serum of patients with recent hemolytic streptococcal infections and in that of patients with rheumatic fever there are usually large amounts of an antibody (antifibrinolysin) which neutralizes the activator and prevents it from dissolving fibrin.[135, 1a] This also suggests that patients with rheumatic fever have recently suffered from a hemolytic streptococcal infection.

BACTERIOSTATIC ANTIBODIES. Streptococcus A type specific bacteriostatic antibodies have been found to develop in the blood of patients following group A streptococcal infections.[76, 118] The presence of these antibodies is demonstrated by the phagocytosis of virulent strains of A streptococcus which produce large amounts of type specific M (protein) antigen. Similar bacteriostatic antibodies have been demonstrated in the blood of patients with acute rheumatic fever.[131]

Concomitant with the rise in individual antibodies in cases of rheumatic fever there is an increase in serum gamma globulin.[68]

(7) *Sulfonamide and Penicillin Prophylaxis.* Additional support for the hemolytic streptococcal theory was found in the observations of sulfonamide prophylaxis of streptococcus A throat infections and rheumatic fever. Small, continued doses of a sulfonamide or penicillin were found to prevent hemolytic streptococcal pharyngeal infections and also the recurrent attacks of rheumatic fever that frequently follow these pharyngeal infections in rheumatic subjects (p. 766). Rapid control of epidemics of hemolytic streptococcal infection in military barracks by chemotherapy or antibiotics was followed by a sharp diminution in new cases of rheumatic fever.[65] On the other hand neither the sulfonamides nor penicillin has a favorable effect on rheumatic fever, once it has developed.

(8) *Hyaluronidase and Antihyaluronidase.* The collagenous ground substance which is primarily affected in rheumatic fever contains hyaluronic acid as a principal substrate. Many strains of hemolytic streptococci have been found to produce hyaluronidase,[26, 60] an enzyme capable of hydrolyzing hyaluronic acid and decreasing its viscosity, thereby favoring the passage of pathogenic microorganisms into collagen tissue. Thus Guerra[59] demonstrated that a suitable dye, when injected intradermally with hyaluronidase, spread to a much greater extent than when the dye was injected with saline. In patients with rheumatic fever, there was much more diffusion of the dye than in normal controls. Hyaluronidase was interpreted as a "spreading factor" produced by hemolytic streptococci and accounting for its invasiveness of collagen tissue in rheumatic fever. Salicylates were found to inhibit the hyaluronidase and reduce its spreading effect.[59] This could account in part for the favorable action of salicylates in rheumatic fever. The significance of these observations remains to be determined.

A mucin clot prevention test has been based on the ability of hyaluronidase to destroy the capacity of protein-hyaluronic acid complex to form a typical mucin clot on addition of acetic acid. Human serum contains a substance (antihyaluronidase) which inhibits the action of hyaluronidase on mucin clot prevention. The mean titer of antihyaluronidase in the sera of patients with early active rheumatic fever was found to be higher than that of sera from patients with subsiding or inactive rheumatic fever, hemolytic streptococcal disease or nonstreptococcal infectious diseases.[42, 110]

Critique of the Hemolytic Streptococcal Theory. In brief, the hemolytic

streptococcal theory maintains that rheumatic fever is a phase in the life history of pharyngeal infection with streptococci of Group A. Phase I is the primary hemolytic streptococcal infection, phase II a subsequent quiescent period of one to three weeks, phase III the active rheumatic inflammation and phase IV an inactive rheumatic stage which may become activated again by a hemolytic streptococcus infection. Variations in the strain, type and virulence of the infecting streptococcus and differences in susceptibility of the host account for the failure of many hemolytic streptococcal infections to be followed by active rheumatic disease.

However, it appears improbable that the hemolytic streptococcus, per se, is the causative organism in cases of rheumatic fever:

(1) Blood cultures during active rheumatic fever are almost always negative; when positive, a nonhemolytic streptococcus is the microorganism usually obtained.[80] Hemolytic streptococci have not been isolated with any regularity from rheumatic tissues.

(2) Rheumatic fever or rheumatic heart disease has never been reproduced convincingly by hemolytic streptococci or indeed by any other means. The spontaneous occurrence in rabbits and guinea pigs of myocardial inflammatory foci resembling Aschoff bodies is a source of misinterpretation of experimental results in these animals. Neither could the claims of the experimental production of rheumatic fever in guinea pigs by the combination of vitamin C deficiency and the injection of hemolytic streptococci be accepted or substantiated.[125]

(3) The above-mentioned findings of hemolytic streptococci in throat cultures in relation to subsequent attacks of rheumatic fever, and the findings of hemolytic streptococcal antibodies have been contradicted, especially by Wilson and her associates.[148] The frequent disappearance of hemolytic streptococci from the throats of rheumatic patients during the quiescent interval (phase II) and during rheumatic activity (III) is another objection levelled at the hemolytic streptococcal theory. The purported absence of throat infections prior to some attacks of rheumatic fever and the frequent failure of rheumatic subjects to suffer a recurrence despite a streptococcal throat infection are additional criticisms of the theory.

However, the seeming occurrence of rheumatic fever without previous throat infection might be controverted if bacteriologic studies could be made with more regularity. Moreover, the frequent absence of rheumatic activity after an hemolytic streptococcal infection and the occasional absence of significant levels of antistreptolysins during rheumatic activity may be dependent on the particular type of hemolytic streptococcus responsible for the throat infection. Better understanding of the bacteriologic and immunologic characteristics of the individual strains of streptococcus A may disclose the exact types which are etiologically related to rheumatic fever. At present, the weight of evidence strongly supports the hypothesis that the hemolytic streptococcus (Group A) or specific types of this streptococcus are important in initiating or precipitating the first or subsequent attacks of rheumatic fever in susceptible individuals. At the same time it appears very improbable that the hemolytic streptococcus is the specific causative organism directly responsible for rheumatic fever.

2. Allergic Theory of Rheumatic Fever. The allergic theory has been proposed to account for many of the gaps or inconsistencies in the streptococcal theory and for the failure to isolate a specific causative organism from the

blood, joint effusions or the affected tissues in cases of acute rheumatic fever and rheumatic heart disease. It should be emphasized that the allergic theory is not a unitary concept, for some of its advocates believe that rheumatic fever is an allergic response to infection with hemolytic streptococci, others that it is an allergic response to any of the streptococci, hemolytic or nonhemolytic, or even to other microorganisms, and finally some have concluded that rheumatic fever may result from sensitization to many types of foreign proteins, bacterial or nonbacterial.[81]

Still another variant proposes that rheumatic fever is caused by autoantibodies. Cavelti[11] produced antibodies to the heart and connective tissue as well as kidney of rats and rabbits, by repeated injections of emulsions of the homologous tissues in conjunction with killed streptococci. On the basis of his experimental observations and the finding of autoantibodies to human heart in the blood of 75 per cent of patients with acute rheumatic fever, Cavelti suggested the following hypothesis of rheumatic fever: Streptococcal substances in combination with connective tissue, including that of the heart, produced an autogenous antigen (streptococcus-heart), which incited the development of specific antibodies. The latter were thought to precipitate the rheumatic lesion by reacting with the streptococcal-tissue antigen.

Evidence for the Allergic Theory. The positive evidence for the allergic theory consists of: (1) clinical and pathologic analogies with serum sickness and other "allergic" diseases, (2) skin tests denoting bacterial hypersensitivity and (3) experimental and pathologic evidence suggesting that rheumatic lesions are due to protein hypersensitivity.[81, 1]

(1) An analogy has been drawn between serum sickness which is due to foreign protein sensitization and rheumatic fever. In the former there is a characteristic latent period of ten to twenty-one days between the injection of foreign serum and the development of serum sickness; in the latter there is a similar interval between the pharyngitis, tonsillitis or scarlet fever and the subsequent appearance of active rheumatic fever.[123] In both diseases, fever, nonsuppurative arthritis and cutaneous lesions are characteristic manifestations.

Support for the allergic theory of rheumatic fever is also seen in many similarities between this disease and tuberculosis and syphilis. Allergic responses to the specific causative organism are considered to account for many of the findings in tuberculosis and syphilis. Rheumatic fever, like these latter diseases, is represented as a chronic infectious disease affecting numerous organs and associated with specific granulomatous lesions.

(2) The reports mentioned above of cutaneous hypersensitivity of rheumatic patients have been interpreted as supporting the allergic theory. According to the individual observer, the hypersensitivity is caused by preceding infection with hemolytic streptococci or nonhemolytic streptococci or both. More recently Taran et al.[132] found a higher incidence of positive skin tests among rheumatic than among nonrheumatic children to the injection of the purified type-specific M proteins obtained from Group A hemolytic streptococci. Variations and inconsistencies in previous reports of skin tests may depend on the particular bacterial protein used in the testing material.

(3) The injection of streptococci into lower animals has been followed by lesions which have been reported by some observers as similar to or identical with those seen in allergic diseases and in rheumatic fever. Reactions similar to those of tuberculin allergy were induced by repeated intracutaneous inocula-

tion of rabbits or intraperitoneal injections of guinea pigs with alpha, beta or gamma streptococci.[150] Lesions resembling those of rheumatic fever were produced experimentally by Klinge[73] and by Vaubel[140] in the heart, joints and coronary arteries following the injection of horse serum. Similar reports were made more recently by Fox and Jones,[37] by Rich,[113] and by Moore et al.[93]

Rich and Gregory[114] found lesions of periarteritis nodosa in cases of serum sickness and sulfonamide reactions, and produced similar lesions experimentally by the injection of horse serum into previously sensitized rabbits. Rich[113] also produced lesions which he considered typical of rheumatic fever in the hearts of rabbits similarly treated with horse serum. Because of the evidence that periarteritis nodosa is an "allergic" disease and because Rich found that both periarteritis nodosa and rheumatic fever could be produced by the same technic of foreign protein sensitization, he concluded that rheumatic fever is also an allergic disease with lesions due to anaphylactic hypersensitivity in a sensitized individual.

These interesting observations may however be viewed with skepticism as regards the identity of the experimental lesions with those of rheumatic fever. Furthermore Robinson[116] was unable to confirm the reported observations of Rich[113] with respect to the myocardial lesions induced by injecting horse serum; and Clawson[16] reported experimental observations which were at variance with both Rich and Robinson. Up to the present time the results of experimental attempts at producing rheumatic fever are too inconsistent to provide support for any specific etiologic theory of rheumatic fever.

3. Nonstreptococcal Theories of Rheumatic Fever. Besides the streptococci, a variety of organisms have at times been implicated as the specific causative agent of rheumatic fever. In particular, the failure to isolate with regularity a specific bacterial agent has suggested that the responsible cause may be an unidentified virus. Schlesinger, Signy and Amies[124] observed particles resembling virus elementary bodies, obtained by high-speed centrifugation of pericardial or pleural fluid from persons with acute rheumatic pericarditis. Saline suspensions of these bodies were agglutinated by sera of patients with active rheumatic fever. Kuttner and Krumwiede[75] suggested that the cause of rheumatic fever was an unidentified virus, acting in association with hemolytic streptococci. Virus bodies were observed by Coles[23] in Giemsa-stained spreads of pericardial fluid from cases of acute rheumatic fever, but similar bodies were seen in the pericardial fluid of 25 of 50 nonrheumatic cases. Eagles and Bradley[31] also demonstrated the nonspecific character of these agglutination reactions.

Claims for the tubercle bacilli[82] and for pleuropneumonia organisms have not been substantiated.[121]

Preliminary reports of a beneficial therapeutic response of rheumatoid arthritis and rheumatic fever to the administration of compound E of the adrenal cortex suggest a new approach to the study of the etiology of rheumatic fever.[62a]

Predisposing Causes of Rheumatic Fever

Geography and Climate. It has long been recognized that rheumatic fever is essentially a disease of temperate climates and is relatively rare in the tropics. The disease is common in Great Britain and France but rare in the tropical possessions of these nations.[2] In Canada and the United States the incidence of

rheumatic fever diminishes progressively as one proceeds southward.[126] Paul and Dixon[104] found the incidence of rheumatic heart disease ten times as frequent in a group of Indian school children living close to the Canadian border (Wyoming and Montana) as among a similar group near the Mexican border (Arizona). An analysis of numerous Army Air Force posts in the United States in the last World War revealed a very high incidence of rheumatic fever in the northern Rocky Mountain regions and Great Lakes as compared to those near the Mexican border and Gulf of Mexico.[65] Coburn[17] emphasized the rarity of rheumatic fever in Puerto Rico and noted the subsidence of symptoms and absence of recurrences in rheumatic patients transported there from New York. On the other hand I have frequently observed active rheumatic fever in Puerto Ricans who have come to live in New York City.

The significance of a possible relationship between geography and climate and the incidence of rheumatic fever must be evaluated with caution. In the first place there is much less certainty than formerly as to the relative rarity of rheumatic fever and heart disease in southern and tropical countries. Chavez[12] reported a surprisingly high incidence of rheumatic heart disease in Mexico and other observers have discovered rheumatic fever or heart diseases in subtropical or tropical places in which the disease was considered almost nonexistent, such as Ceylon, India, China, Costa Rica, Hawaii and Panama. In the second place, admitting differences in incidence depending on geography and climate, it is uncertain whether such correlation depends on meteorologic conditions (temperature, rainfall, barometric pressure, etc.), racial differences, economic and dietary differences, bacteriologic flora and immunity, or especially crowding, with its predisposition to the spread of infection.

Season. The greatest incidence of rheumatic fever is in the colder and wetter months of the year, and most commonly in January, February, March and April.[103] In Great Britain a high incidence has been reported as beginning somewhat earlier, e.g., October or November, and continuing through the spring.[45] In India, Kutumbiah[77] observed no seasonal variation in the occurrence of rheumatic fever. The seasonal relation to streptococcal or other respiratory infections has been repeatedly noted. The seasonal incidence is probably not related to cold or dampness as such for in World War I rheumatic fever occurred much less commonly among troops in action in cold, damp trenches than among those in warmer and drier but overcrowded barracks.

Urbanization. Rheumatic fever occurs much more frequently in industrialized, well populated cities than in rural areas.[62] The correlation is not linear for the mortality rate from rheumatic heart disease is higher in Denver, Colorado, than in many much more populous and industrialized cities. To the extent that urbanization predisposes to rheumatic fever, it appears that crowding and the consequent spread of infection are the important factors.

Economic Status and Housing. The Factor of Crowding. British investigators have emphasized the greater frequency of rheumatic fever among the lower economic groups.[128, 45, 4, 66] In one series there was an incidence of 13.1 per cent rheumatic patients in the outpatient department and only 0.7 per cent in private practice. Nevertheless, there is some evidence that rheumatic fever, unlike tuberculosis, does not strike the very destitute but rather those above this level. In this country poverty has not appeared to be a significant predisposing factor.

The question of housing is closely related to economic status. Rheumatic

fever has often been associated with dampness in general and damp housing in particular. Geographic studies of the incidence of rheumatic fever in London show a close correlation with proximity to the course of old streams.[133] In New York, Ingermann and Wilson[67] found the smallest percentage of cases in districts farthest from the river fronts. A high incidence of rheumatic fever has been reported in houses judged to be damp by British sanitation inspectors[141] and particularly among individuals residing in basements or ground floors without cellars beneath them. Other reports minimize the importance of dampness in housing.[91]

It is probable that economic status and housing are predisposing factors in rheumatic fever, chiefly in so far as they lead to crowded living conditions. An analysis of rheumatic heart disease in Bristol, England, revealed that its incidence was closely related to crowding in the home.[107] The factor of crowding and consequent predisposition to the spread of infection was also considered significant in explaining the greater frequency of rheumatic fever in northern as compared with southern United States,[104] and in accounting for the occurrence of epidemics in boarding schools, hospital wards and barracks.[145]

Family Incidence, Heredity and Constitution. A number of investigators have called attention to a significantly high family incidence of rheumatic fever.[13, 122, 67, 105] Cohn[20] stated that 8 to 10 per cent of members of rheumatic families experienced rheumatic fever but only 2.9 per cent of the families of nonrheumatic controls. Similar observations have been made by Massell and Jones[87] and others. A significant familial tendency to rheumatic fever is, however, by no means universally accepted as fact.

A high family incidence has been variously attributed to infectious communicability of rheumatic fever, to similar environmental factors in members of the same family, to hereditary or constitutional susceptibility or to a combination of these. Evidence for frequency of rheumatic fever among certain anthropologic types or in individuals with certain pigmentation of skin, eyes, hair (e.g., red hair) is unconvincing. Wilson[146] and her associates,[147] after many years of careful observation of families with rheumatic fever, have concluded that the susceptibility to this disease is an inheritable characteristic, dependent on a single autosomal recessive gene. However, one cannot minimize the probable importance of the infectiousness of rheumatic fever itself[52] or of preceding respiratory diseases, as well as similar unfavorable environment such as crowding, climate, etc., in explaining a high familial incidence of rheumatic fever.

Age. About 90 per cent of first attacks of rheumatic fever occur between the ages of 5 and 15.[21] More occur between 5 and 10 than between 10 and 15. Less frequently rheumatic fever begins between the ages of 15 and 20, between 1 and 5 or between 20 and 25 or older, in the given order.[62] Thus in its primary stages, rheumatic fever is essentially a disease of elementary school children. The probability of a first attack and the tendency to recurrence diminish significantly after puberty is established. Rheumatic fever among military personnel in the last war occurred chiefly in the youngest recruits; in many of these a careful clinical history and examination usually disclosed a previous attack.

Rheumatic fever is very uncommon in the first two or three years of life. In infancy it is extremely rare; Denenholz and Rambar[27] reported a case in a ten days old infant. Most of the reported cases in infancy are instances of placental infection from rheumatic mothers or infection in the sucklings of

such infected mothers. The youngest case I have seen concerned a seventeen months child who, two days after a fall, suffered pain in an ankle associated with fever and pulmonary symptoms. Postmortem examination, shortly afterward, revealed myocardial Aschoff bodies and other evidence of active rheumatic heart disease.

Sex. There is a slightly greater incidence among females, chiefly because of the preponderance of females affected by chorea.[21, 103] Excluding the latter, the incidence is essentially the same in both sexes.

Race. The data are inconsistent regarding racial differences in the incidence of rheumatic fever. Some statistics appear to indicate a greater frequency of the disease among the Irish, the Anglo-Saxons and the Jewish races. The incidence among Negroes has been found to be higher, equal to or lower than that among white subjects in different locations. While rheumatic fever is rare in Puerto Rico, I have seen rheumatic fever frequently and in severe form in recent Puerto Rican immigrants who have settled in New York. Boas[9] has drawn an analogy between the severity of rheumatic fever in Puerto Ricans and that of other infectious diseases attacking a nonimmune population.

Nutrition. Undernutrition and improper nutrition have been considered as factors predisposing to rheumatic fever. Epidemiological and experimental evidence that a deficiency of ascorbic acid may be an etiologic factor was presented by Rinehart, Connor and Mettier.[115] The diet of patients with rheumatic fever has been reported to be deficient in vitamins A and D and in calcium and phosphorus.[106] However, rheumatic fever has occurred with great frequency in naval and other military installations among young recruits who were well nourished and properly fed. It is improbable that nutrition is either an essential or important factor in the development of rheumatic fever. However it may be a nonspecific factor in determining resistance to infection.

Physical Factors. Trauma. Frequently the localization of rheumatic arthritis is determined by physical strain. Thus the joints of the lower extremities are more apt to be affected when the patient's occupation demands excessive walking or standing; the joints of the hands may be involved among typists or seamstresses.

The French school of physicians repeatedly emphasized the importance of trauma in determining the onset or recurrence of rheumatic fever. The most striking instances are those in which, within a few days after a fall or other injury, acute rheumatic fever develops first in the joint nearest to the injured region.[43] The factor of coincidence is difficult to exclude.

PATHOLOGY

General Features

Pathologically, rheumatic fever is characterized by *proliferative* and *exudative inflammation,* involving primarily collagen tissue and its ground substance. There is a pronounced tendency to affect tissues lined by endothelium, including blood vessels, endocardium, pericardium and synovia.

The *primary rheumatic lesion* is characterized by swelling and occasional necrosis of collagen or of the ground substance between the collagen fibrils. This undergoes a hyaline or eosinophilic alteration, sometimes inaccurately termed fibrinoid degeneration. Klinge[73] refers to this early change as the rheumatic "früh-infiltrat," in analogy with tuberculosis, but the use of this expres-

sion in rheumatic fever may be confusing. The swelling of collagen is associated with an exudative reaction consisting of edema, lymphocytes and other round cells, and less characteristically of polymorphonuclear and plasma cells.

The *proliferative reaction* is characterized by granulomatous formations, which in their most characteristic form are called Aschoff bodies (infra). This proliferative phase is often so dominant that Fahr[34] refers to rheumatic fever as rheumatic granulomatosis. The proliferative reaction consists of focal (Aschoff bodies) or diffuse cellular collections including numerous round cells, macrophages, fibroblasts and peculiar large cells which may be multinucleated. The exudative and proliferative reactions are not sharply demarcated, both occurring simultaneously in varying intensity.

The *final stage of rheumatic inflammation* is characterized by healing and scar formation. In the valves such scarring results in serious deformities. The above-mentioned exudative and proliferative inflammatory lesions represent the *active stage* of rheumatic fever. In the *inactive stage,* the inflammatory reaction is absent and only the healed scars are observed.

Cardiac Lesions

Localization of Rheumatic Lesions. Rheumatic cardiac lesions are characterized by their widespread distribution in the endocardium, myocardium, pericardium and conduction system. This is the basis for the term *rheumatic pancarditis.* The detailed studies of Gross and his associates on rheumatic lesions in their numerous sites of localization have provided an extensive anatomic armamentarium with which to establish the essential rheumatic nature of cardiac disease, even in the absence of Aschoff bodies or a typical clinical history of rheumatic fever.

Specific and Nonspecific Lesions. The specific lesions are the Aschoff bodies which are described in the next section. It is generally agreed that the presence of myocardial Aschoff bodies is definite evidence of rheumatic heart disease.[38, 55] The granulomatous lesions described as occurring in animals following various experimental efforts to produce rheumatic fever do not show the specific characteristics of the Aschoff bodies.

The *nonspecific but rather characteristic lesions* include the macroscopic and microscopic alterations in the left atrium, the vascularization and inflammation of the valves (including the valve rings), the valvular verrucae, the valvular deformities, the pericardial lesions, myocardial scars and certain lesions at the root of the aorta and pulmonary artery.

Some lesions are very characteristic, if not specific. Among these may be mentioned the banded appearance and palisade formation of the cellular exudate in the left auricular endocardium, the subendocardial reduplications in the left atrium and valves, and the vascular lesion termed the intimomuscular elastic variety.

The Myocardial Aschoff Body. Aschoff bodies are rounded or spindle-shaped submiliary nodules of microscopic size. Rarely conglomerations of Aschoff bodies form grossly visible nodules which appear as pearly white streaks. They occur in any portion of the heart, but most often in the subendocardial regions of the left ventricle and frequently in close proximity to small blood vessels. They primarily involve the interstitial tissue.

The structure of the Aschoff body undergoes a life cycle corresponding with the clinical course of the disease.[55] The earliest development, representing a

pre-Aschoff body stage, is characterized by swelling of the collagen and local accumulations of small round cells, apparently lymphocytes. At this stage argentophilic fibers can be demonstrated by Pap's stain between the swollen collagen fibers and close to the round cells. At this stage also the lesion is not specific for rheumatic fever and this must be kept in mind in the evaluation of similar experimental lesions.

The typical specific Aschoff body presents certain definite features regardless of the stage of its life cycle:

(1) There are characteristic cells with abundant, somewhat basophilic cytoplasm and irregular boundaries ("ragged edges"). The cytoplasm may appear as irregular, broken syncytial masses of indefinite outline.

(2) Many of these cellular nuclei have an owl-eye or "target" appearance. The nuclei are of circular shape, with deeply staining nuclear membrane and a dark, sometimes stellate ("wheel-spokes") nucleolus.

(3) There are multinucleated giant cells, with usually two or three, and occasionally seven or more round or oval nuclei, situated in the center of the cell.

(4) Other cells, within the Aschoff body proper, resemble the fibroblast or fibrocyte, while still others are small cells with large, solidly staining polymorphous nuclei (pyknotic cells).

(5) Among the characteristic owl-eyed, giant, fibrocytoid and pyknotic cells is swollen collagen which has become disintegrated and granular. Silver impregnation reveals argentophilic fibers.

(6) The Aschoff body proper, composed of the above elements, is usually surrounded by a mantle of polymorphonuclear cells, lymphocytes, plasma cells, fibroblasts or occasional eosinophils.

While the above elements are always present, their relative proportions and their figurative arrangement undergo variations according to the acuity or chronicity of the disease, the looseness or compactness of the affected tissues, and perhaps also according to the immunological state of these tissues. Eventually the Aschoff body is converted into a characteristic spindle-shaped, flame-shaped or triangular scar lying between the muscle bundles and surrounding blood vessels.[73]

Pericardial Lesions. Pericarditis is one of the most frequent and most characteristic of rheumatic lesions. The occurrence of acute pericarditis and of adherent pericardium was described by Baillie[5] and other early writers. The typical reticulated, curdled appearance of fibrinous pericarditis was described by Corvisart and Laennec, the latter noting its similarity to "bread and butter," an expression retained by Hope and all textbook writers after him. Gross lesions are almost invariably present either diffusely or as localized patches of fibrous thickening.

In the *active cases,* there may be a universal fibrinous exudate with thickening, glazing and adhesions. There is a variable amount of straw-colored, turbid fluid containing many shreds of fibrin. Occasionally the effusion is fibrinopurulent. With recurrent attacks, the pericardium is converted into a thick, shaggy membrane with numerous tenuous adhesions. In the *inactive cases,* the pericardial layers are thick and adherent to each other and to neighboring extracardiac structures. Frequently there is complete obliteration of the pericardial sac, but in the early stages there may still be serofibrinous or serohemorrhagic exudate sacculated between adhesions. Calcification may occur. Occasionally, there are peculiar polypoid and cystlike formations.

Microscopically, pericardial lesions are found in almost 100 per cent of the *active cases.*[41] The earliest lesions are represented by swelling and degeneration of collagen in the lamina propria, inflammation and vascularization of the same layer and of nearby portions of the subjacent adipose layer. Soon there is an exudation of fibrin which, together with the subjacent inflammation, represents the nonspecific reaction of a serous membrane to an injury. The mesothelial cells may become completely desquamated and may form pseudo-gland structures or polypi. With recurrent infections and in later stages of the active cases, there is marked thickening of the pericardial membranes with layers of fibrin, inflammatory exudate and granulation tissue. The pericardial layers become adherent and the pericardial cavity is obliterated.

In the *inactive cases,* the pericardial layers are thickened and adherent due to the formation of considerable fibrous tissue. There may be inflammatory residua, consisting of infiltrations of small round cells in the deeper layers of the lamina propria and adjacent layers and an increased number of vessels showing structural changes.

Rheumatic Lesions in the Left Atrium. Detailed descriptions have been reported by MacCallum[83] and by Gross.[54]

Macroscopic Appearance. The characteristic lesions are usually situated on the posterior wall of the left atrium just above the posterior cusp of the mitral valve. They consist of an irregularly raised series of ridges and mounds forming tawny-gray patches, or occasionally flat yellow plaques. In the inactive stage the lesions become grayer and more translucent and the endocardium may appear wrinkled. There may be hyaline plaques, occasionally with lime. Macroscopic lesions in the left atrium are reported to occur in 29 to 80 per cent of rheumatic hearts, the higher percentage in the active cases.

Microscopic Appearance. The auricular endocardium becomes widened by edema and cellular infiltration. The collagen undergoes swelling and degeneration and assumes a banded appearance. The various inflammatory cells are often oriented characteristically at right angles to the auricular lumen and may be "palisaded" in layers along the bands of swollen collagen. The normal avascular endocardium becomes highly vascularized by the penetration of capillaries at right angles from the subendocardial layer.

The *inactive or healed lesion* consists of pronounced widening of the auricular endocardium by fibrous tissue. A considerable portion of the thickening is due to characteristic endocardial "reduplications"[54] composed of newly formed layers of tissue arising from the normally inconspicuous subendothelial mesenchyme. These wide reduplications are demarcated by condensations of elastic tissue, each one representing an individual attack of rheumatic fever.

Lesions of the Valves. Rheumatic valvular lesions have been described in detail by Coombs,[24] Swift,[130] Gross and Friedberg[57] and others.

Active Stage. The most frequent lesion is the thickening of the valve cusp and its loss of transparency. The most characteristic lesion is the vegetation or "verruca." The verrucae appear as rows of fine, glistening grayish or yellow wartlike vegetations on the closure line of the mitral and aortic, and much less commonly on the tricuspid or pulmonic valves, in the given order of frequency. Not infrequently the tricuspid leaflets and occasionally the pulmonic leaflets disclose distinct microscopic lesions when they appear normal on gross examination. The normally concave, scalloped margins of the auriculoventricular valves are thickened and straightened. The auricular surface may show gross vascularization.

Microscopically, the earliest valvular lesions occur at the "ring" or attachment of the cusp to the fibrous annulus.[130, 57] The close anatomic relationship of the four fibrous annuli to each other accounts for the ease of extension of the inflammatory process from one ring to the others. The ring becomes vascularized and swollen with edema and inflammatory cells. The inflammatory process extends throughout the cusp and produces a valvulitis before there are verrucae.[78] The typical rheumatic proliferative and exudative lesions occur. The cusp becomes thickened by edema, capillary vascularization and cellular infiltration (lymphocytes predominantly and occasionally polymorphonuclear leukocytes, but Aschoff bodies, fibroblasts, macrophages and plasma cells also occur).

The verrucae, in active cases, consist of hyaline eosinophilic material resulting from swollen, degenerated collagen and disintegrated cells near the surface of the valve. The verruca arises chiefly from swollen, degenerated valvular substance which is extruded beyond the surface of the cusp. However, platelet thrombus and a small amount of fibrin, arising from the blood stream, may be deposited as a cap on the valvular component of the verruca.

Inactive or Healed Stage. The valve cusps become greatly thickened and opaque, and may be rigid and deformed. In the active stage the thickening is due to edema and inflammatory cells; in the healed stage, to excessive formation of fibrous tissue. Vascularization becomes grossly visible. The vegetations are organized and appear firmer, duller and gray. There may be two or rarely more rows of verrucae, denoting successive attacks. The thickening of the distal half of the atrioventricular cusps and the superimposed healed verrucae may form a well-marked "shelf" of tissue overhanging the chordae tendineae.

The *atrioventricular cusps* may become shortened due to the contraction of scar tissue and the rolling of the thickened free margin; occasionally they are elongated by newly formed collagenous tissue at the free margins, supplemented by the absorption of chordae. The latter are thickened at their heads of attachment (ham-shaped), shortened, and fused to each other as well as to the leaflets. Consequently the papillary muscles are brought closer to the margins of the valve cusps. The latter may become fused, which with the shortening of the chordae results in a stenotic, funnel-shaped valve. Infiltration with lime increases the rigidity and stenosis.

The *semilunar valves* likewise become thickened and shortened. Their free margins become rolled and inverted toward the sinus pocket (entropion). The inversion of the nodulus aurantii produces a characteristic notching. The semilunar folds are either approximated to the free margin or disappear. The commissures are joined by adhesions, separated by a delicate slit. Insufficiency or stenosis of the valve usually results. Gross vascularization and calcium infiltration are frequent, the latter accentuating the functional disturbance of the valve.

Microscopically, the valve cusps appear thickened by fibrous tissue resulting from organization of the inflammatory exudate and by subendothelial reduplications. Thick muscular vessels pervade the cusp, but there are few inflammatory cells, chiefly lymphocytes. The verrucae are organized, hyalinized and covered by endothelium.

Lesions of the Coronary Arteries and Their Branches. Lesions of the vascular apparatus, including the coronary arteries, represent a fundamental feature of the pathology of rheumatic fever,[142, 58] but it is doubtful whether they are of sufficient importance to account for clinical phenomena. The usual

evolutionary degenerative changes in the coronary vessels are accelerated and intensified in cases of rheumatic fever; therefore coronary arteriosclerosis may occur much earlier in such cases. This is exemplified by a seventeen months old child whom I observed with acute rheumatic fever, whose heart at postmortem examination disclosed a complete thrombosis of a major coronary artery.

There may also be nonspecific degenerative or inflammatory lesions which are occasionally grossly visible in the small myocardial arteries but which are more often of microscopic size. The gross lesions may be those of polyarteritis nodosa[40] while the microscopic lesions consist of intimal proliferation and necrosis, endarteritis verrucosa or polyposa, or fibrin-like occlusions which become organized and recanalized.[142] Gross, Kugel and Epstein[58] described intimomusculoelastic lesions of the small coronary arteries characterized by intimal proliferation of smooth muscle and elastic tissue, and considered almost specific for rheumatic fever.

Lesions in the Aorta and Pulmonary Artery. Klotz[74] gave the first detailed descriptions of rheumatic vascular lesions including those of the aorta. Pappenheimer and von Glahn,[100] Gross[53] and others also contributed studies of rheumatic aortic lesions. Occasionally there are macroscopic brownish ridges or plaques on the inner surface. The usual lesions at the root of the aorta are microscopic and situated chiefly in the outer portion of the media and in the adventitia, following the course of the vasa vasorum. There are collections of lymphocytes, polys and Aschoff bodies, edema, pronounced capillarization and scarring and disruption of the elastica. Similar lesions are also found occasionally in the pulmonary artery and have been described by Paul,[101] Chiari,[14] and others.

Lesions in the Atrioventricular Conduction System. The frequent occurrence in rheumatic fever of arrhythmias and especially of partial heart block may be due in many instances to anatomic lesions in the conduction system. Gross and Fried[56] found exudative or vascular lesions within the bundle of His or surrounding tissue in 66 per cent of active cases.

Extracardiac Lesions in Rheumatic Fever

Subcutaneous Nodules. Pathologically these are proliferative lesions, consisting of collagen swelling and degeneration, inflammatory cells, edema and vascularization similar to that in other rheumatic lesions.[90] Often there is a necrotic center containing fibrinoid material. Structures resembling Aschoff bodies have been reported. The nodules may show scarring, calcification and rarely deposition of cartilage or bone. Allowing for the difference in milieu, the subcutaneous nodule corresponds in structure and specificity to the Aschoff body. Some investigators have reported histologic resemblances to the nodules found in rheumatoid arthritis,[25] but I believe there are essential pathologic differences.[71]

Pulmonary and Pleural Lesions. Pulmonary and pleural lesions occur frequently in rheumatic fever, but there is disagreement as to the specificity of a rheumatic pneumonia.[102, 97, 32, 98, 69] A healed (proliferative) phase with extensive fibrosis and an active exudative phase have been described.[95]

The lungs have been described as characteristically large, purplish-red, beefy and of india rubber consistency.[97] The involved areas are nonfriable and homogeneous and present atelectasis and splenization rather than hepatization. *Microscopically,* the affected parts show edema and hyperemia, local atelectasis

and widespread focal hemorrhagic lesions involving lobules or groups of lobules.

The alveolar walls are thickened by proliferating capillary endothelial cells and fibroblasts, and the interstitial tissue is thickened by edema and inflammatory and mononuclear cells.

The alveolar lumina are filled with edema fluid and frequently by a hemorrhagic and fibrinous exudate. Mononuclear cells predominate and include desquamated epithelial cells and phagocytic cells.

Vascular lesions of the capillaries and small arteries consist of intimal thickening, hyaline thrombi, occasional scarring or necrosis of the media and adventitial and periadventitial cellular infiltrations.

A hyaline membrane lining the bronchioles and alveolar ducts is a characteristic feature, and possibly represents a transformed fibrinous exudate.[88]

A fibrinous or serofibrinous pleural exudate may be present. Proliferative and exudative "rheumatic-like" lesions have been described, but no definite Aschoff bodies have been demonstrated.

Other Lesions in Rheumatic Fever. Abdominal pain may be related to necrotizing arteritis of visceral arteries[40] or other vascular lesions. Serous peritonitis with vascular lesions and inflammatory exudate in the subperitoneal tissue has been described by Rhea[112] in fatal cases of rheumatic fever. Specific rheumatic lesions have been reported in the peritonsillar tissue[47] and in the regional lymph nodes draining rheumatic tissues.[39]

Cerebral lesions associated with chorea include a disseminated meningoencephalitis affecting chiefly the corpus striatum.[50] A meningoencephalitis has also been reported in rheumatic heart disease without chorea.[64] Bruetsch[10] has repeatedly reported and emphasized the occurrence of cerebral lesions and cerebral sequelae of rheumatic fever. In particular, he observed a "rheumatic" obliterating arteritis involving the small meningeal and cortical vessels with consequent infarction and softening of cerebral tissue. Certain cases of mental illness and epilepsy were attributed to such rheumatic cerebral lesions.

Relation of Rheumatic Fever to Rheumatoid Arthritis

There are many differences between the clinical manifestations and course of rheumatic fever and of rheumatoid arthritis, chief of which is the frequency of cardiac involvement in the former. In recent years, necropsy findings have been reported which suggest that cardiac lesions of rheumatic fever are encountered with significant frequency in cases of rheumatoid arthritis. Rosenberg and associates[117] recorded the finding of rheumatic heart disease in 16 (53 per cent) of 30 autopsied cases of rheumatoid arthritis and Young and Schwedel[149] in 25 (66 per cent) of 38 such cases. In evaluating these reports, it is important to know the exact criteria employed for the diagnosis of rheumatic heart disease and the incidence of such "rheumatic" lesions in control groups. Thus according to criteria used by Hall and Anderson,[61] rheumatic stigmata in presumably normal hearts were found microscopically in 90 per cent of 112 hearts, and "Aschoff bodies" in 30 per cent of the hearts. If such criteria are employed, the finding of rheumatic lesions in cases of rheumatoid arthritis loses significance. In general there appears to be a definite distinction between the pathologic lesions usually associated with rheumatic fever and those of rheumatoid arthritis.[7] The clinical course and electrocardiographic findings in rheumatic fever are not observed with rheumatoid arthritis.

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32

RHEUMATIC FEVER

Clinical Picture

INTRODUCTORY

The clinical picture of rheumatic fever may be dominated by cardiac or extracardiac symptoms. But even when the obvious symptoms are extracardiac, one can almost always assume cardiac involvement. In adults the most frequent and characteristic clinical picture of rheumatic fever is that of an acute migrating polyarthritis with fever and other evidences of toxemia. In children the articular symptoms are often less flagrant and less widespread, and the clinical picture may be dominated by extra-articular manifestations including chorea, abdominal pain, cutaneous and subcutaneous lesions and cardiac disease. Atypical, mild and subclinical forms of rheumatic fever are not uncommon among both children and adults.

Rheumatic fever is characterized by its chronicity and tendency to recurrent exacerbations.[25] The recurrences, like the original attack, consist of any one of the variety of clinical forms which rheumatic fever may assume. Thus the first attack may be one of chorea, the second polyarthritis and the third pancarditis. Or cardiac disease may be present from the beginning, each new attack leading to further myocardial and valvular damage. The acute attacks generally last one to three months but occasionally there are fulminating cases ending fatally in several days or weeks. Usually the disease enters a chronic afebrile stage in which there may be no symptoms unless an acute exacerbation occurs.

Rheumatic heart disease is considered as being *active* or *inactive* depending on the persistence or subsidence of acute rheumatic inflammation. This distinction is important in the management of the patient and the evaluation of his prognosis. As in tuberculosis, inactive rheumatic heart disease is not synonymous with cure, for there is a great tendency to recurrence of the active disease. The symptoms of active rheumatic heart disease are due to the inflammatory lesions in the heart and the associated toxemia. The symptoms of inactive heart disease are due to the scars and deformities produced by healing of the inflammatory lesions and to the associated chemical changes in the myocardium. These alterations may be insufficient to produce clinical symptoms during long intervals of the inactive stage.

MODES OF ONSET

The onset may be insidious or acute. Vague prodromata may precede the acute outbreak. When rheumatic fever follows severe exposure or chilling, symptoms of the disease occur suddenly within forty-eight hours. More often and characteristically a hemolytic streptococcal sore throat, tonsillitis or scarlet fever is followed by a latent period of one to four weeks, after which symptoms of rheumatic fever appear. Following are some of the more common ways in which rheumatic fever and rheumatic heart disease begin:

1. *Arthritis and fever* are the commonest symptoms of onset.[3, 79] Occasionally there is no definite arthritis, but only fleeting multiple joint pains without noticeable inflammation, or pain and disability involving a single joint.

2. *Cardiac symptoms* may first attract attention to the patient's illness. The chief complaint may be precordial pain due to a fibrinous pericarditis or a pericardial effusion, or else there is palpitation resulting from tachycardia and extrasystoles. Occasionally dyspnea, edema, abdominal distress and other symptoms of myocardial failure appear to be present from the beginning.

3. *Chorea* may be the first and sole evidence of the initial attack of rheumatic fever. Occasionally this follows a physical or psychic trauma. Cardiac lesions and other rheumatic symptoms may develop concomitantly with this initial attack or more often in subsequent rheumatic episodes.

4. *Abdominal and gastrointestinal symptoms.*—Vague, fleeting abdominal pains are uncommon prodromal symptoms of rheumatic fever. Occasionally the abdominal pain is severe and simulates an acute surgical complication.

5. *Fever of obscure origin* associated with malaise, headache or anorexia may be present for some weeks before other evidences of rheumatic fever appear.

6. Rheumatic heart disease may be *latent,* its recognition depending on discovery of a valvular lesion at routine physical examination. Or cardiac failure may develop in an individual who gives no history of rheumatic fever. The rheumatic etiology of the failure is suggested by the finding of evidence of valvular disease.

7. Rarely the first symptoms of rheumatic fever are subcutaneous nodules, cutaneous lesions such as erythema marginatum, or profuse epistaxis.

Nonspecific prodromata have been mentioned as preceding the well defined symptoms, particularly in children. The symptoms in the prodromal stages of rheumatic fever include: pallor, fatigability, anorexia, digestive disturbances, abdominal pain, loss of weight, nervous irritability, so-called "growing pains" in the joints and adjacent muscles and tendons, respiratory infections, adenopathy and low grade febrile attacks.

CLINICAL FORMS OF RHEUMATIC FEVER

The lesions of rheumatic fever may affect almost every organ. Correspondingly, the clinical symptoms and combinations of symptoms are remarkably protean. However, certain common clinical forms of the disease may be distinguished according to the predominant symptoms. As the disease becomes prolonged or acute exacerbations ensue, these clinical forms tend to intermingle.

1. The *articular form* is the most distinctive and the most easily recognized. Fever and arthritis may occur suddenly after chilling and exposure, or after a free interval of one to three weeks following an upper respiratory infection. The onset of fever and polyarthritis may be more gradual, the temperature ris-

ing as the inflammation spreads from joint to joint until many of them have been successively involved. When fully developed, the clinical picture is that of a general infection with toxemia, chilliness (or occasionally rigors) and severe sweats, but the acute, migrating polyarthritis is the dominant feature. This form is most clearly observed among adults. Among children, arthritis is frequent but is neither as severe nor as widespread. The articular form of the disease as it occurs in adults usually runs its course in three to five weeks, and is more apt than other forms to leave the heart unaffected. This may be due to the frequent erroneous diagnosis of rheumatic fever in cases of rheumatoid or other types of arthritis in adults.

2. The *cardiac form* is the most serious clinical variety of rheumatic fever. It is especially frequent in children. The illness may present any one of the modes of onset listed above, but evidences of cardiac disease rapidly dominate the clinical picture. Fever and other signs of infection are present. Frequently there are symptoms of fresh pericarditis or pericardial effusion. The heart becomes enlarged. Evidences of left and right heart failure may become prominent. Valvular disease may develop under observation or may represent residua of a previous attack. Joint symptoms, cutaneous lesions, pulmonary disease are overshadowed by the pancarditis. Cardiac failure may subside, and recur with renewal of the infection. Death may result. If the patient recovers, he is left with an enlarged heart, badly functioning valves, an injured myocardium and pericardial adhesions.

3. The *typhoidal or influenzal form* embraces the cases in which fever and toxemia are the dominant features. This clinical form includes particularly cases whose essential rheumatic nature is unrecognized. When vague respiratory, abdominal or gastrointestinal symptoms are associated with fever and toxemia, the patient is mistakenly treated for grippe, pneumonia or typhoid fever. Fever of obscure origin may be the only evidence of a recurrent bout of rheumatic fever and particularly of a reactivation of rheumatic carditis. The diagnosis often remains obscure during weeks of fever, weakness or prostration until a definite polyarthritis develops or endocardial or pericardial lesions are discovered.

4. The *pulmonary form* refers to cases with predominant pleural and pulmonary symptoms. Fever, generally of high degree, is invariably present. Pericarditis and other cardiac symptoms are usually and extracardiac symptoms are sometimes associated. While chest pain, cough and respiratory distress may be present, the physical signs of pulmonary consolidation, fibrinous pleuritis or pleural effusions often predominate over subjective symptoms.

5. The *abdominal form*. Occasionally abdominal and gastrointestinal symptoms not only initiate the rheumatic attack, but continue as its essential features.[2] A number of unrelated clinical syndromes are simulated. Abdominal pain and tenderness, fever, nausea and vomiting and leukocytosis lead to a diagnosis of acute appendicitis or some other acute surgical abdominal disease and a laparotomy may be performed. The association of abdominal pain, fever, diarrhea and bloody stools simulates dysentery or ulcerative colitis. The diagnosis of rheumatic fever in such cases is necessarily obscure, unless the patient is a known "rheumatic" or subsequently develops arthritis, subcutaneous nodules, valvular disease or other definitive rheumatic symptoms.

6. *Chorea* may be classified as a *neurologic form* of the disease. Its rheumatic nature is denoted by the later development of other classic features of rheumatic fever in one half to three quarters of the cases of chorea.

7. *Mixed forms.* Too much stress must not be laid on these clinical forms as separate entities, for there is much overlapping. Furthermore, it should be emphasized that while any one of these forms may temporarily dominate the clinical picture and mask the rheumatic nature of the attack, additional forms and more typical features evolve with progress of the disease. Thus mixed forms are quite frequent. When there are multiple acute attacks, each one may be associated with a different clinical form.

Rheumatic fever in childhood is hardly to be distinguished as a separate clinical variety of rheumatic fever. It deserves special mention because in childhood the more obvious features of the disease are often absent or insignificant and the diagnosis is more likely to be overlooked. The following points require emphasis: The onset is usually insidious and characterized by vague symptoms such as pallor, fatigability, nervous irritability, arthralgias and myalgias ("growing pains"), anorexia and digestive disturbances. Varied manifestations such as epistaxis, chorea, subcutaneous nodules, erythema marginatum or other cutaneous lesions, and severe unexplained anemia are frequent. These symptoms as well as cardiac disease develop more frequently in children than in adults. On the other hand, children rarely develop the full picture of acute polyarthritis, although mild and localized articular symptoms are frequent.

Atypical Forms in Adults. Observations during World War II disclosed the relative frequency of rheumatic fever among young adults in the military forces.[143, 106, 121] Usually the clinical picture was characterized by fever and an acute polyarthritis. Not infrequently, however, there was only mild pain and stiffness in a single joint, without systemic symptoms; or there were only chills and fever; or vague muscular pains, backache and urinary symptoms; or abdominal and gastrointestinal symptoms. In some of these reported cases, one may question the diagnosis of rheumatic fever despite electrocardiographic abnormalities.

GENERAL COURSE OF RHEUMATIC FEVER

In general the course of rheumatic fever may be classified under four general types:

1. The *recurring type* is characterized by an acute attack which subsides in one to two weeks in mild cases or in one to three months in severe cases. Subsequently there is complete inactivity for one or more years. After two to five such attacks, the disease remains inactive. This is the most common form.

2. The *chronic inactive type* in which carditis is part of the initial attack but there is no recurrence of activity thereafter.

3. The *chronic active type* in which there are troughs of relatively little clinical activity but in which there is never complete subsidence. From time to time there are clinical exacerbations. Progressive cardiac failure leads to fatality after many months or after several years.

4. The *acute fulminating type* is uncommon and is characterized by high fever and toxemia with severe carditis and heart failure and a fatal issue after several weeks or months.

THE INDIVIDUAL SYMPTOMS OF RHEUMATIC FEVER

These are classified as: (1) general, nonspecific evidences of infection, and (2) local manifestations, which are more characteristic and depend on the involvement of numerous individual organ systems.

General Symptoms

The general symptoms may be very vague, particularly in the prodromal period and in children. The affected child tires easily, appears pale and listless, eats little, loses weight and seems to be wasting. He may be brought to the doctor because of "nervousness," pallor and undernutrition, poor schoolwork, or because it is feared he is suffering from pulmonary tuberculosis. When the disease is well defined, there are distinct symptoms of a general infection.

Fever. This is an almost constant symptom except in chorea. It is the most practical and reliable guide to persistence of infection when the local symptoms have disappeared. The temperature curve is rather variable but four general types may be mentioned: (1) an irregular, well marked febrile course lasting from a week or two to a month or two; (2) a continuous low grade febrile or subfebrile course; (3) a continuous low grade curve, accentuated by more definite bouts of fever lasting several days; (4) an infrequent hyperpyrexia.

1. Irregular, but pronounced febrile course. This is the most frequent temperature curve and is associated with well developed arthritic or visceral lesions and with prolonged spreading infection. The temperature ranges up to 103° F., occasionally higher, with daily variations of 1° to 3° F. Irregularity in the curve is due to the thrust-like manner in which the disease suddenly attacks a new joint or some new organ or recurs in some site in which the infection has previously subsided. Further irregularity is due to modification of the natural course of the disease by the modern universal usage of salicylates.

Before the use of salicylates, characteristic types of the fever curve were described. Friedländer[39] described monocyclic, polycyclic and continuous varieties. In the "monocyclic" variety which composes about 60 per cent of cases (Griffith[45]), there is a progressive steplike rise in temperature lasting about a week, each elevation corresponding to the involvement of new joints. As the infection involves new joints, it subsides in the original sites which are not implicated again. The temperature falls gradually when no further joints are affected. The entire cycle lasts one to two weeks. In the "polycyclic" variety, cycles such as that described come and go with relapses, the same or new joints being involved. The course is more severe and more prolonged than in the monocyclic variety; pericarditis, pneumonitis and heart failure are common. In the "continuous" temperature curve, there is a prolonged irregular elevated temperature.

The duration of the fever is quite variable. In abortive cases or mild recrudescences, it only lasts a few days. In a well marked attack, the duration may vary from a week or two to one or more months. Gull and Sutton[49] using only mint water to treat their cases concluded that the average duration of uncomplicated rheumatic fever was nineteen days. Pribram[99] reported that of 457 cases treated with and without salicylates 27 per cent had fever for two to three weeks, 16 per cent for three weeks or more, and 3 per cent for more than thirty days. In the remaining 54 per cent the duration of fever in a single acute attack was less than two weeks. The entire illness generally lasted one and one half to two times as long as the fever. The administration of salicylates reduced the temperature but not the duration of the attack, which ranged between 14.7 and 47.5 days. Similarly, Miller[84] found an average duration of 33 days in 3500 cases of rheumatic polyarthritis, the period being the same whether or not salicylates were administered.

2. Continuous low grade febrile or subfebrile course. The temperature may rise only to between 100° and 101° F. and may even be normal at certain times of the day. Obviously the discovery of such mild degrees of fever requires rectal thermometry and often also continuous charting of temperature several times daily. This type of fever may be present in the prodromal stages before arthritis or cardiac disease develops. When local symptoms abate, the high irregular curve described above may be transformed into a low grade fever. Failure to reach the normal baseline indicates persistence of infection despite the absence of local symptoms. In known cases of inactive rheumatic heart disease, such mild degrees of fever may represent the sole clue to recurrent rheumatic infection.

3. Continuous subfebrile course with acute exacerbation. This type of curve is seen during relapses after apparent subsidence of the acute symptoms. The temperature does not quite fall to normal. After several days of low grade fever, the temperature suddenly rises to 102° or 103° F. and persists with daily remissions for several days. This rise may be associated with or followed by an obvious development of an acute arthritis, skin lesions or a pulmonary or cardiac complication. If there is no new obvious symptom, the sudden rise in temperature demands careful and repeated examinations to determine the presence of carditis, pneumonia or pleurisy. If the relapses are repeated, the temperature may again resume the irregular type of curve.

4. Hyperpyrexia is a rare complication of rheumatic fever.[41] It is to be distinguished from the terminal rise in temperature to 106° or 107° F. occasionally seen in fatal cases. In rheumatic hyperpyrexia, the temperature rises to between 107° and 110° F. and occasionally to 111° F. or higher. Most often, it occurs in the second or third week of the first attack, sometimes when the infection is subsiding and convalescence has begun. It is associated with symptoms of cerebral rheumatism. Delirium at night (when not due to salicylates) and excessive micturition are premonitory symptoms. The patient may develop convulsions, squint, risus sardonicus, opisthotonos, deafness, irregular respiration, lividity and progressive coma. Death is the rule when the temperature exceeds 107° F. Rheumatic hyperpyrexia has been practically eliminated since the introduction of salicylates.

Persistence of Activity without Fever. Fever is an almost invariable accompaniment of active rheumatic disease. However, occasionally the temperature is normal despite the presence of active infection. In chorea, which is generally accepted as a manifestation of active rheumatic fever, the temperature may remain normal throughout the attack. In the prearthritic or precardiac stages of rheumatic fever, there is often no fever although progressive anemia, fatigability, loss of weight, etc., indicate active disease. Similarly there may be no fever toward the end of a rheumatic attack when all symptoms have disappeared, yet there may be persistent rheumatic inflammation as indicated by tachycardia, leukocytosis and increased rate of sedimentation of red blood cells. There may be little or no fever with subcutaneous nodules although these represent active rheumatic disease. Thus, while fever is a valuable guide to rheumatic inflammation, its absence is not conclusive that activity has subsided.

Pulse. A regular tachycardia of 100 to 140 is a common sign of rheumatic activity. The tachycardia is often out of proportion to the degree of fever. The pulse is full, bounding, easily compressible and often dicrotic. In convalescence, there may be bradycardia. When the temperature has reverted to normal either

spontaneously or with salicylates, a persistent tachycardia usually indicates continued rheumatic activity, probably within the heart.

Respiration. Increased respiratory rate may accompany the rise in temperature but is not significant. Marked tachypnea has been mentioned by Pribram[99] as resulting from the pain of inflamed joints. Most of the respiratory abnormalities encountered in rheumatic fever are due to local infection of the lungs, pleura or upper respiratory tract, or to left heart failure.

Sweating. Profuse sweating has been described as a characteristic feature, particularly of the articular form of the disease. In recent years this manifestation has appeared to be less prominent. It may be limited to the night or occur throughout the day and night, and may become severe enough to cause maceration of the skin. The use of salicylates accentuates the diaphoresis. Crops of sudamina are common.

Loss of Weight and Undernutrition. These are frequently present in the prodromal stages of the initial and subsequent attacks. In the fully developed attack, the weight loss may be extreme due to pain, anorexia and toxemia. But I have seen a persistent drop in the weight curve as a result of active disease even when subjective symptoms have been controlled by rest in bed and medication. Weight curves, especially in children, are valuable guides to the progress of the rheumatic patient and to the persistence of active inflammation. A rising weight curve in the course of a rheumatic attack is often the harbinger of subsiding activity and beginning convalescence.[81] Conversely, I have seen the reversal of such a curve without apparent cause during convalescence, followed in a few days by a rise in temperature and the recurrence of local symptoms.

Local Symptoms

The numerous symptoms of rheumatic fever are evidence of widespread involvement of many organs. The most characteristic symptoms are due to lesions of the heart (pancarditis), the joints (arthritis), the skin (subcutaneous nodules) and the nervous system (chorea). But almost every organ may be affected, as shown by the widespread vascular lesions described. Many of the lesions, however, fail to cause obvious symptoms.

Of 1108 rheumatic patients under the age of twelve seen in a first attack, carditis was present in 61 per cent, arthritis in 57 per cent, chorea in 56 per cent and subcutaneous nodules in 9 per cent.[98] In a similar series observed by Coombs[28] in an outpatient department, 72.5 per cent showed cardiac disease, 61.8 per cent arthritis, 47.2 per cent chorea, and 4 per cent subcutaneous nodules. Coburn[22] listed the frequency of various symptoms in 162 patients presenting the "rheumatic state" as follows:

	Per Cent
Polyarthritis	85
Pancarditis	65
Recurrent epistaxis	48
Muscle ("growing") pains	47
Attacks of pallor	36
Severe headaches	33
Cardiac pain	32
Chorea	30
Abdominal pains, nausea, vomiting	20
Erythema marginatum	17
Subcutaneous nodules	13.6

These and other statistical analyses indicate the great frequency of cardiac disease in rheumatic fever. Because of its frequency and seriousness as compared with other symptoms, cardiac disease is the central feature of any consideration of that disease. Our presentation of individual symptoms is therefore concerned essentially with cardiac manifestations. Extracardiac symptoms are presented primarily from the point of view that they may be the earliest or most prominent clues leading to the diagnosis of rheumatic heart disease or to the detection of a reactivation of rheumatic cardiac infection.

Cardiac Symptoms. Rheumatic cardiac symptoms are classified according to their occurrence in the (a) *active* or (b) *inactive* stage of the infection. They are further classified according to the anatomic site of the lesions into: (1) *endocardial* and *valvular,* (2) *myocardial* and (3) *pericardial* manifestations.

It should be noted that in both the active and inactive stages cardiac lesions may be present without producing overt symptoms. The latter depend on the extensiveness of the anatomic lesions and their situation in critical cardiac sites. Thus, extensive involvement of the auricular endocardium may be clinically imperceptible, while only moderate disease of the valvular endocardium occasions definite manifestations. Similarly a slight degree of edema, cellular infiltration or scar formation implicating the bundle of His gives rise to gross clinical and electrocardiographic abnormalities, while more extensive myocardial lesions in less vital situations are asymptomatic. Widespread pericardial adhesions may go unrecognized during life while a few bands obstructing the blood flow through the vena cava may produce a definite clinical syndrome. In the absence of symptoms or a history of rheumatic fever, rheumatic heart disease is discovered accidentally on physical examination or sometimes for the first time at postmortem examination.[38] Occasionally the presence of rheumatic heart disease is first disclosed when the patient is observed because of the development of auricular fibrillation, congestive heart failure or bacterial endocarditis.

It cannot be emphasized too strongly that so long as there is evidence of active rheumatic disease in any form, there is constant danger of cardiac damage. This danger should not be overlooked when the administration of salicylates has reduced or dissipated the fever, eliminated gross evidence of arthritis and given the patient a sense of well being. It appears most probable that salicylates neither preclude the development nor reduce the incidence of cardiac infection in rheumatic fever. Therefore the peril of cardiac injury is not over with the abatement of gross clinical manifestations. The disappearance of active disease must be proved by sensitive laboratory methods (p. 745).

Active Stage of Rheumatic Heart Disease. 1. ENDOCARDITIS AND VALVULITIS. The clinical signs of endocarditis result essentially from inflammation of the valve ring and cusp. Edema, cellular infiltration and vascularization rapidly produce swelling and dilatation of the ring permitting regurgitation of blood. Extension of the inflammatory process to the valve cusp leads to incomplete or improper opposition and closure, abnormalities which are accentuated by the deposition of verrucae at the closure line.

The development of endocarditis is documented by: (1) an alteration in cardiac sounds, (2) the occurrence of new cardiac murmurs and (3) a change in the character of murmurs previously present.

Very early, there is a loss of the distinctive muscular quality of the first

sound at the apex. It may become prolonged and diminished in intensity.[66] It has been described as "impure," "murmurish" or "mushy." Sometimes there is a splitting or reduplication of the second sound at the apex, an occurrence emphasized by Sansom[112] and Cheadle.[20]

Blowing systolic murmurs occur early and frequently.[90] They are located at the apex, to the left of the sternum, at the level of the fourth rib, over the pulmonic or aortic area or over an extensive precordial area. They are best heard when the patient is supine. These systolic murmurs may indicate early organic involvement of the valvular endocardium, but must be distinguished on the one hand from functional murmurs due to the associated fever or anemia, or cardiorespiratory factors, and on the other hand from the organic murmurs of chronic valvular deformity which evolve later in the course of the disease.[97] It is usually impossible to distinguish the systolic murmur occurring early in active rheumatic fever from functional murmurs. Its organic nature may be strongly suspected by its loudness, roughness or blowing quality, long duration, radiation to the left axilla, and persistence despite change of position or respiratory phase. Persistence long after subsidence of rheumatic activity denotes that it is due to an organic mitral insufficiency. The early systolic murmur may completely disappear with subsidence of the active stage of the disease. Occasionally a mid-diastolic apical murmur has been reported as occurring in the early stages of rheumatic fever and disappearing after the rheumatic attack abates.[13] Care should be exercised not to confuse gallop rhythm or a third heart sound associated with a prolonged P-R interval as a diastolic murmur. Subsequently, organic murmurs of chronic valvular disease may or may not develop. Diastolic or presystolic murmurs may replace or become associated with the systolic murmur.

Sometimes signs of organic valvular disease develop early in the course of what appears to be the first active stage of the disease. In such instances one is at a loss to determine whether these signs are the result of a previous unnoticed attack or whether they can develop with unusual rapidity in the course of the first one. In occasional instances, murmurs of organic mitral or aortic disease have been reported to develop within a few weeks after onset of the rheumatic attack, under the careful observation of competent examiners.

2. PERICARDITIS. In the active stage, two clinical varieties of pericarditis may be distinguished: (1) *acute fibrinous pericarditis* and (2) *pericarditis with effusion.*

Postmortem studies disclose that organization of the inflammatory exudate and the development of adhesions occur even in the active stage, but these give no clinical symptom in the active disease (p. 707). The incidence of pericarditis in rheumatic fever is variously reported as 3 per cent,[105] 5 per cent[99] and 13 per cent;[28] but in children as a group it is more frequent (25 to 35 per cent[41]). Pericarditis is often overlooked clinically, unless frequent and careful examinations are made. Recent pathologic studies indicate microscopic pericardial lesions in almost 100 per cent of patients dying of active rheumatic heart disease, but clinical evidences were reported only when the lesions were severe and extensive.[37]

When there is clinical evidence of pericarditis, the patient is usually suffering from a serious form of rheumatic heart disease. The recognition of pericarditis should call attention to the underlying myocardial infection. Pericarditis is also associated with other serious visceral rheumatic infections, particularly

pleurisy and pneumonia. The latter may result from direct extension of the pericardial disease. Subcutaneous nodules are said to be associated frequently with pericarditis.

(1) *Acute fibrinous pericarditis.* The essential symptom is substernal, precordial or abdominal pain and the essential sign a pericardial friction rub. A detailed discussion of the symptoms and signs of acute fibrinous pericarditis is presented in Chapter 22.

The occurrence of acute pericarditis is often marked by a rise, sometimes considerable, in the fever curve. In young adults in the army, signs of pericarditis usually developed within a few days after the onset of acute rheumatic fever.[143] Evidence of pneumonia, pleurisy, pulmonary infarction or heart failure often accompanies pericarditis.

(2) *Pericardial effusion* of slight degree is generally associated with acute pericarditis. However, the clinical diagnosis is made with certainty only in the occasional cases with large effusions.

The precordial pain and pericardial rub of the acute fibrinous pericarditis may or may not disappear with the formation of a considerable effusion. The patient may suffer precordial oppression and a characteristic sense of anxiety. Restlessness, insomnia, delirium and other mental symptoms occasionally occur. With large effusions the patient is exceedingly dyspneic and orthopneic so that he must sit upright in bed. He may become cyanotic or flushed, but often he presents an intense pallor. The picture of an intensely pale and dyspneic child sitting up anxiously in bed and complaining of precordial pressure and pain is very suggestive of rheumatic pericarditis with considerable effusion. Dysphagia, aphonia and an irritative cough may result from pressure on the esophagus or recurrent laryngeal nerve. A detailed account of the symptoms and signs of pericarditis with effusion is given in Chapter 22.

3. MYOCARDITIS. Lesions of the myocardium proper are the most important cardiac evidences of active rheumatic fever. Recognition of these lesions requires frequent regular examinations. In the presence of a rheumatic pericarditis or valvular disease, one can practically assume myocardial involvement. An unexplained rise in temperature in the course of rheumatic fever is a significant clue suggesting the necessity of careful examination of the heart. An increased pulse rate is merely evidence of the general infection. But a disproportionate rise in pulse rate or a persistent tachycardia despite a spontaneous or salicylate-induced fall in temperature suggests the presence of carditis.

The patient's *symptoms* may be few or they may be numerous and severe. Precordial pain of variable severity is frequent. This pain occurs without exertion and may be due to an associated pericarditis or to disease of the coronary branches or root of the aorta. It may be mild or, rarely, it may simulate true angina pectoris. Precordial pain should be distinguished from precordial distress due to palpitation and tachycardia, which is common. Other symptoms are due to heart failure.

The *signs* of active rheumatic myocarditis are: changes in heart sounds, rapid cardiac enlargement, evidences of heart failure, disturbances in cardiac rate and rhythm. Electrocardiographic changes also denote myocardial involvement. In the absence of heart failure or arrhythmias, the evidences of myocarditis are not distinctive and are difficult to segregate from those due to the generally associated endopericarditis. Practically, this distinction is unim-

portant, as involvement of any portion of the heart usually indicates a coexisting myocarditis.

The earliest signs of myocarditis are changes in the quality, intensity and pitch of the first sound.[97] This becomes dulled, muffled or almost obscured. It may appear to have the same pitch and quality as the second sound, producing a tic-tac or dup-dup effect (embryocardia) instead of the normal lub-dup or lub-dupt. A blowing systolic murmur may be due to myocardial disease, inflammation of the valve rings and cusps or to other factors (such as fever and anemia) associated with the rheumatic infection. The cardiac impulse is generally diffuse and feeble. But when the acute myocarditis is superimposed on a previously damaged heart with chronic valvular disease and hypertrophy, the cardiac impulse is more apt to be strong and tumultuous.

Evidences of *right and left heart failure* are commonly observed in children with severe forms of rheumatic myocarditis. In adults cardiac failure is often seen in patients with inactive rheumatic heart disease who suffer an acute recurrence. Dyspnea, orthopnea, "cardiac asthma" and cough are the common manifestations of *left heart failure* with pulmonary congestion and edema. An associated pericardial or pleural effusion may contribute to the severity of the dyspnea and orthopnea. Diastolic gallop rhythm is an important sign of left ventricular failure and of myocarditis during active rheumatic fever. However, a presystolic gallop rhythm occurs in the absence of heart failure if the a-v conduction time is prolonged and the auricular sound is audible. It may also be difficult to distinguish a physiologic third heart sound with tachycardia from a significant diastolic gallop rhythm. When *right heart failure* develops, there may be a subsidence of orthopnea. In children, right-sided congestive heart failure may be predominant from the beginning.[134] The patient's extremities become swollen with edema, the liver is enlarged and tender, hydrothorax develops and occasionally there may be ascites. The patient complains of abdominal distress and nausea and he may vomit. Some children present a puffy face as in glomerulonephritis. Unexpected weight gain may precede visible edema. There may be cyanosis of the lips and fingertips if anemia is not too severe. The cervical veins and those of the extremities become distended, and the venous pressure is elevated.

Cardiac enlargement may occur rapidly with active rheumatic heart disease if there is severe myocardial infection with failure. The enlargement may be the result of a previous attack. It can be interpreted as a sign of activity only if it develops or progresses under observation and if there are other evidences of active rheumatic fever. There may be a diminution in cardiac size with subsidence of rheumatic activity and restoration of cardiac compensation.[130]

Disturbances of cardiac rhythm (see also p. 739) are both frequent and valuable signs of rheumatic myocarditis. They may represent the earliest manifestations of cardiac involvement as well as the only evidence of active infection. While the arrhythmias are often clinically recognizable, discovery and confirmation of their exact nature generally requires electrocardiograms, which should be repeatedly recorded. The arrhythmias are discussed under the heading of electrocardiographic changes (p. 738).

Inactive Stage of Rheumatic Heart Disease. The clinical picture of inactive rheumatic heart disease is essentially that of valvular disease of the heart. Proof that the disease is inactive consists of negative observations. The symptoms of acute endocarditis, myocarditis and pericarditis are absent as well as the extra-

cardiac symptoms of active rheumatic fever. Even in the absence of such clinical symptoms, there may be active rheumatic infection as indicated by various laboratory and electrocardiographic examinations as well as by pathologic studies post mortem. For practical purposes rheumatic heart disease is considered as being inactive when in addition to the absence of fever, tachycardia and other symptoms of active rheumatic infection, the white blood count, rate of sedimentation of red blood cells and repeated electrocardiograms are normal.

Subjective symptoms may be entirely absent in the inactive stage of rheumatic heart disease. Physical signs, however, are generally well defined. Both the physical signs and the subjective symptoms when present are those of chronic valvular heart disease, with or without heart failure. These are discussed in detail in the chapters on the individual valvular lesions (Chapters 26 to 29). In a series of 2476 persons with rheumatic heart disease rejected by draft boards in five large American cities, there were signs of mitral insufficiency alone in 750, of mitral stenosis alone in 750, of aortic insufficiency alone in 208, of aortic stenosis in 72, and of combined mitral and aortic valvular disease in 628.[74]

Complications of Rheumatic Heart Disease. The chief complications of rheumatic heart disease are: (1) cardiac failure, (2) auricular fibrillation and other arrhythmias, (3) subacute and acute bacterial endocarditis, (4) embolization. More rarely there are: an anginal syndrome with or without coronary sclerosis or occlusion; essential hypertension; hyperthyroidism (Graves' disease); Adams-Stokes syndrome. Many other so-called complications are really essential elements of the rheumatic infection or represent unrelated intercurrent infections.

1. *Cardiac failure* occurs in one half to three quarters of all cases of rheumatic heart disease. It is the most frequent cause of death in both the active and inactive stages of the disease. In children and young adults, cardiac failure is usually due to active inflammation of the heart muscle. This is supported by the finding of Aschoff bodies and other evidence of acute rheumatic fever in 75 to 95 per cent of the hearts of patients dying of heart failure in the first two decades of life and in a substantially lower percentage of those dying in later age periods.[107, 27] The mechanical effects of the acute and chronic lesions in the valves, myocardium and pericardium and the associated cardiac enlargement may play an important contributory role in producing failure.

After the age of forty, active rheumatic disease is a relatively uncommon factor in producing heart failure. Coronary arteriosclerosis with severe narrowing or occlusion becomes an important contributory or precipitating cause. Cardiac compensation is frequently established and well maintained once adolescence is past and rheumatic recurrences become uncommon. However, this compensation is accomplished by cardiac hypertrophy and increased cardiac work, both of which require a supernormal blood supply. With the advent of severe coronary arteriosclerosis, relative myocardial anoxemia disrupts these compensations and induces cardiac insufficiency. Acute infections of all kinds, the development of an arrhythmia with rapid ventricular rate or pulmonary embolism is the trigger mechanism precipitating heart failure.

Recurrent right heart failure is characteristic of mitral stenosis and tricuspid disease. Patients with aortic insufficiency rarely suffer from right heart failure until the final episode. However, evidences of chronic left heart failure, includ-

ing dyspnea with or without orthopnea and "cardiac asthma," may be present for many years before the end.

2. *Auricular fibrillation* complicates about one fifth to one half of the cases of chronic rheumatic heart disease, but particularly those with mitral stenosis, and those in which there is chronic congestive heart failure. Occasionally auricular fibrillation occurs as a transient phenomenon during an acute attack of rheumatic fever. It is an important factor both in the onset and progression of cardiac failure and in the development of auricular thrombi with subsequent embolization. Auricular fibrillation is thus not in itself fatal and is often compatible with comfortable life for many years.

3. *Subacute bacterial endocarditis* and less often acute bacterial endocarditis tend to occur on valves showing the active or inactive lesions of rheumatic disease. They develop in 10 to 20 per cent of cases of rheumatic heart disease (p. 777). The use of antibiotics has greatly diminished the frequency with which bacterial endocarditis is a fatal complication. Bacterial endocarditis is a significantly more frequent complication of aortic insufficiency than of mitral stenosis.

4. *Embolization* in rheumatic heart disease is usually a complication of mitral stenosis, and especially when the latter is associated with auricular fibrillation or cardiac failure. It may, however, occur quite unexpectedly in a patient with inactive rheumatic heart disease with regular rhythm and well compensated circulation. It occurred in 1.8 per cent of 600 cases reported by Coombs,[28] settling nine times in a cerebral and twice in an abdominal or femoral artery. In the brain, the middle cerebral artery is generally occluded, sometimes with sudden fatality. Usually, however, there is a crossed spastic hemiplegia with or without aphasia. Loss of function is not usually as severe as in a hemiplegia due to cerebral thrombosis or hemorrhage, and restoration of function may be almost complete after several months.

Embolization at the bifurcation of the abdominal aorta or of the large vessels of the extremities may lead to gangrene. While amputation is sometimes necessary, the limbs are not infrequently spared by conservative treatment alone, or occasionally by operative removal of the clot. Often embolization is merely an incident in advanced heart failure. In such cases the patient's prognosis and the choice of treatment for the embolus may depend not on the embolization but on the severity of the failure and its response to therapy.

Multiple pulmonary infarcts are frequent[139] as a result of embolization from mural thrombi of the right auricle. However, more often than is generally recognized, pulmonary embolism and infarction in mitral stenosis are secondary to phlebothrombosis of the vessels of the lower extremities and not to auricular thrombi. Chest pain, cough and hemoptysis with or without cyanosis and dyspnea are the classic symptoms. But embolization may be signalized instead by a rise in temperature, transient dyspnea or a precipitation or exacerbation of congestive heart failure. Renal and splenic emboli are uncommon in rheumatic heart disease. In the absence of auricular fibrillation the occurrence of cerebral, peripheral or visceral embolization should be attributed not to rheumatic heart disease itself, but to a complicating bacterial endocarditis.

Angina pectoris is occasionally encountered in the active and inactive stages of the rheumatic heart disease. In young persons it is associated with aortic stenosis or in an uncommon and distinctive form with aortic insufficiency (p. 591). Occasionally it accompanies mitral stenosis, but it is doubtful

whether there is more than a coincidental relationship (p. 574). In older persons it is usually due to coronary artery sclerosis or to calcific aortic stenosis. Coronary thrombosis may occur at an earlier age in rheumatic persons because of predisposing rheumatic vascular lesions. *Essential hypertension* is occasionally associated with rheumatic heart disease, occurring frequently with *mitral stenosis* in patients over forty years of age (p. 580). *Graves' disease* may represent an accidental association. However, French clinicians believe that it may be a direct result of rheumatic infection because hyperthyroidism occasionally develops in the course of acute rheumatic fever. *Effort syndrome* is common in rheumatic heart disease. It is generally difficult to evaluate the relative importance of the actual cardiac disease and of the superimposed neurosis in the production of symptoms.

Extracardiac Manifestations. *Arthritis.* Arthritis is the most constant and most conspicuous local manifestation of the disease, and particularly among adults may dominate the clinical picture. It may, on the other hand, be relatively insignificant or absent. Among children the arthritis, when present, is often atypical. The inflammatory phenomena are relatively mild; only a single joint or two may be affected; or there may be arthralgias without clinical evidence of inflammation.

Characteristically, there is a symmetrical polyarthritis, primarily affecting large joints, with rapid development and subsidence of inflammatory phenomena, and successive involvement of new joints as inflammation in the others regresses. But in many cases reported among military forces only a single joint was affected.[106] The joints most frequently involved are the knees, ankles, shoulders and wrists. However, almost any joint may be implicated, including the small joints of the hands and feet, the elbows, hips, vertebrae, the sternoclavicular and temperomandibular and crico-arytenoid joints, and even the symphysis pubis. Trauma and strain appear to play a role in determining the affected joints.[40] Occasionally the onset of arthritis is observed in a joint immediately after injury to that joint.

The symptoms vary considerably in severity and consist of pain, redness, swelling, increased warmth of the skin overlying the joint, and disability. With the onset of arthritis, there is a rise in fever and an intensification of any other general symptoms. Characteristically the affected extremities are held in flexion and abduction. The pain may be so intense as to make the weight of the bedclothes or jarring of the bed intolerable. Swelling is due chiefly to edema of the periarticular tissues, but in the large joints there may be considerable intra-articular effusion with fluctuation. In the knee joint one may obtain a patellar click.

The acute symptoms, including swelling and effusion, generally respond remarkably to the administration of adequate doses of salicylates, but there may be a slight persistent residual pain and swelling. Inflammation in a given joint may develop fully in a few hours. Its subsidence is more gradual, requiring between one day and one week and occasionally longer.

The synovial fluid is a pale yellow fluid which may be clear or slightly cloudy and may contain some flakes. There is an early predominance of polymorphonuclear leukocytes with a few mononuclear cells and undifferentiated young connective tissue cells. Later there are numerous clasmatocytes containing degenerated cells and debris.[83] Suppuration does not occur except by secondary infection with pyogenic organisms. Claims of the development of

chronic rheumatoid arthritis with deformity as a result of rheumatic arthritis may be questioned. Such a development is remarkably rare if it occurs at all. This fact is a strong argument against a purported identity or relationship between rheumatic fever and rheumatoid arthritis.

Tendinitis, Myositis, Tenosynovitis, Bursitis. Pain in the juxta-articular region may be due to inflammation of neighboring tendons and muscles. Lesions resembling or identical with Aschoff bodies have been observed in tendons, striated muscle and fascia.[43] Myalgias, particularly of the hamstrings in the popliteal space and of the neck muscles, are not uncommon. They are responsible for the "growing pains" in children which should not be confused with the more significant rheumatic arthritis.[52, 120] Atrophy of disuse may occur in muscles adjoining inflamed joints. As I have pointed out with Gross,[36] *polymyositis* may occur when periarteritis nodosa is associated with rheumatic fever. Tendon sheaths as well as tendons may become inflamed. In *tenosynovitis* of the hand, considerable effusions may occur. Characteristic swellings on the dorsum of the hand due to such effusions have been pictured by Garrod[41] and by Klinge.[68] I have seen a severe acute tenosynovitis of the flexor tendon of the right middle finger develop rapidly and subside in three or four days in a twenty-four year old man with valvular heart disease who suffered an acute recurrence of rheumatic fever with arthritis, and pleural and pericardial effusions. I have also seen an acute olecranon *bursitis* in a twenty-eight year old rheumatic patient who developed an acute recurrence with cardiac failure. The aspirated fluid was turbid and contained 2500 cells per cubic millimeter, but no organisms. While allegedly characteristic histologic lesions have been described, it is doubtful whether the bursitis and tenosynovitis are essentially rheumatic manifestations.

Subcutaneous Nodules. These nodules represent one of the pathognomonic features of rheumatic fever and occur in 5 to 20 per cent of cases.[7, 65, 53, 126] They are essentially a manifestation of the disease in childhood, but may develop in young adults. While they may appear in connection with any other rheumatic symptoms, their seriousness lies in their association with severe cardiac lesions, which arise sooner or later in most cases. Cheadle[20] assigned them an ominous prognosis because he observed that there was frequently a fatal pericarditis. However, I have repeatedly seen children with rheumatic fever and nodules recover and experience a favorable clinical course. It is important to recognize these nodules because in some of the attacks they may represent the only local manifestation of rheumatic infection, as in the following case I observed:

A three year old child was running a temperature between 99.5° and 100.5° F. and was found to have subcutaneous nodules. A diagnosis of rheumatic fever was made from this alone. The diagnosis was confirmed six months later when, while the patient was suffering from pallor, loss of appetite and loss of weight, the nodules reappeared but without fever or leukocytosis. Examination revealed a large heart and signs of mitral stenosis, pleural and pericardial effusions. Four years later the nodules recurred in association with polyarthritis, erythema annulare and urticaria. Post mortem, there was active rheumatic heart disease, mitral stenosis, cardiac hypertrophy and adherent pericardium.

The nodules are grayish, translucent, conical or rounded elevations of circular or oval outline varying in size from that of a pinhead to about 2 cm. in diameter. They are situated subcutaneously, unattached to skin so that the skin can be moved freely over the nodule. They tend to occur over bony prominences

and may be attached to fascia, aponeuroses (especially the galea aponeurotica), tendons, and periosteum (skull). The back of the elbow, the bony prominences on the dorsum of the hand or foot, the malleoli, patella, skull, spines of scapula and of vertebrae are favorite sites of localization but the clavicles, ribs, crests of the ilia, sternum, acromium and rarely the flexor tendons of the hand may also be involved. They tend to assume a symmetrical distribution. They vary in number from a few to over one hundred at a time. As with other rheumatic symptoms, there is frequently a characteristically rapid evolution and disappearance of nodules followed by recurrence in new locations. Because of their occasional evanescence, they may be overlooked. Usually, however, because of recurrences, nodules may be observed for weeks or months. There is no redness and usually no pain or tenderness. (The pathology of subcutaneous nodules is discussed on p. 710).

Cutaneous Lesions. The most significant cutaneous lesion is the lesion variously termed *erythema annulare,* e. marginatum, e. circinatum, or e. gyratum according to its configuration.[71, 1, 95, 64] I believe that this lesion is specific for rheumatic fever and is similar in importance to the subcutaneous nodule as a clue to the presence of the disease, the probability of cardiac involvement and the persistence of rheumatic activity. A characteristic histologic picture has been described.[19] As Cheadle[20] pointed out, erythema annulare and subcutaneous nodules are often present simultaneously. Coburn[22] found the former in 17 per cent of his series of cases, a frequency which was slightly higher than that of the subcutaneous nodules. Couper[29] observed an incidence of only 1.9 per cent.

Characteristically the erythematous lesions occur on the trunk, but may appear on the extremities. They begin as reddish or violaceous macules or papules, 1 to 5 mm. in diameter (erythema papulosa), at which stage they are nonspecific. They develop rapidly, literally under one's eyes, into much larger lesions which, by clearing in the center, form circles or segments of circles which join or intersect to trace various types of scalloped, serpentine or crescentic patterns. At their margins, the lesions are pale pink or dull red, sharply circumscribed and slightly elevated; the centers are flat and colored by a faint brown pigmentation. The lesions disappear almost as rapidly as they develop, only to reappear in new crops.

The rheumatic significance of various other cutaneous lesions encountered in questionable. *Urticaria* is, of course, not specific, but I have observed it developing in definite relation to attacks of rheumatic fever. Various other erythemas reported in association with arthritis are not examples of rheumatic fever but belong to the group described by Osler[88] as erythema with visceral lesions. *Erythema multiforme,* except in so far as it may include erythema annulare, is not related specifically to rheumatic fever and its appearance is coincidental. Diffuse *petechiae* (very rarely white-centered) are occasionally observed but widespread purpura is not a feature of the disease.[58] Most cases of purpura with arthritis or arthralgias are instances of Schönlein's disease (peliosis rheumatica) and are mistakenly called rheumatic fever. *Erythema nodosum* sometimes reported as appearing in rheumatic fever is, I believe, either a coincidence or a nonspecific toxic manifestation.[63, 96] The painful *ephemeral nodules* described in the French literature probably represent the so-called Osler nodes[76] in subacute bacterial endocarditis (p 788).

Chorea and Other Neurologic Symptoms. The essentially rheumatic nature

of chorea minor (Sydenham) is no longer questionable.[127] Hughes and Brown,[56] who early emphasized its relationship to polyarthritis and endocarditis, found evidence of rheumatic infection in 85 per cent of their cases of chorea. Like the subcutaneous nodules with which it is frequently associated, chorea is essentially a manifestation of rheumatic fever in childhood. In young male adults in the army in World War II, chorea was observed very rarely in association with rheumatic fever.[143]

It may be the first symptom and is frequently complicated or followed by carditis.[116] Among 1181 rheumatic children studied by Kaiser,[62] chorea was the original expression of the disease in 326 or 28 per cent. Carditis was associated or developed subsequently in 58 per cent. Coombs[28] observed carditis in 76 per cent of cases and Osler[89] reported the cardiac valves intact in only 8 per cent of 125 fatal cases of chorea. Chorea occurs preponderantly among females. In pregnancy it is occasionally observed in a severe form (chorea gravidarum);[140] artificial abortion or premature induction of labor may be required.

There has been some question as to the occurrence of a nonrheumatic, possibly psychogenic chorea. According to Coburn[23] and Kagan and Mirman,[60] at least one half of their observed cases of chorea in children were unaccompanied by other symptoms of rheumatic fever or by the development of cardiac disease. These nonrheumatic cases were characterized by absence of family history of rheumatic fever, absence of preceding respiratory infection, and by normal leukocyte count and sedimentation rate during the attack of chorea.

Clinically, chorea is characterized by constant, uncoordinated, purposeless muscular movements. Its onset is usually insidious, but occasionally it develops immediately after a fall, a trauma, sudden fright or emotional upset. In those cases commencing gradually, the child begins to drop things, spill food and find it impossible to button her clothes. She develops nervous symptoms including irritability, restlessness, sleeplessness, night shrieks and bed wetting. The child may be scolded at school for writing badly or slopping ink. Exaggerated uncoordinated and explosive movements occur spontaneously as well as with muscular effort and are beyond voluntary control. Facial grimaces, rolling of the eyes, tossing of the head and wrinkling of the forehead combine to sketch a distorted picture. The imbecilic appearance which results is belied by the school record of these children, who are often unusually bright and even precocious. Because of the disease, however, they slur their words, phonate badly or may be unable even to speak. They walk improperly, trip themselves, move about irregularly and too rapidly in a manner which the title, St. Vitus' dance, well characterizes.

In severe cases the children must often be kept in a bed with side bars in order to avoid self harm. In such cases also they may be unable to swallow, requiring tube feeding as well as special nursing care because of loss of control of bladder and bowels. Severe cases are easily recognized. In mild ones, there may be only a muscular restlessness. The nature of the disease can be verified by requesting the child to hold her hands steadily outstretched for several minutes, or by holding her hands enclosed in those of the examiner, whereupon the exaggerated twitchings are observed or felt. Chorea may occasionally affect a single extremity or half the body, producing a picture simulating a monoplegia or a hemiplegia.

A moderate leukocytosis and mild fever may be present but in the absence

of other rheumatic manifestations the course is entirely afebrile. Eosinophilia may be present. The attack of chorea may last six to eight weeks or be even more protracted. Recurrences are encountered, sometimes with additional cardiac damage. Death in an acute attack occurs in about 3 per cent of the cases, or in as many as 7 to 20 per cent when chorea occurs during pregnancy.

Pathologically, chorea is a meningoencephalitis involving particularly the basal ganglia, especially the caudate nucleus and putamen in the corpus striatum, and also the internal capsule and cortex.[44] However, the pathologic changes are usually surprisingly mild. The almost invariable complete clinical recovery suggests that the alterations are essentially reversible and therefore are probably predominantly exudative.[82] Vascular lesions, minute areas of softening, degeneration of nerve cells and inflammatory foci have been described.

Cerebral rheumatism was a term formerly applied to psychic disturbances, including personality changes, headache, insomnia, delirium and eventual coma, associated with hyperpyrexia. These manifestations are rare since the use of salicylates, although toxic doses of the latter may also produce delirium and other mental disturbances. More recently the finding of a chronic obliterating endarteritis (p. 711) in the brains of persons dying of rheumatic heart disease has led to the concept that various clinical forms of rheumatic brain disease are due to these underlying lesions.[16, 17, 135] Rheumatic endarteritis of the brain has been found in 5 per cent of patients in a mental hospital and in 9 per cent of patients with dementia precox. Convulsive seizures (rheumatic epilepsy) have also been attributed to rheumatic cerebral lesions.[15] These interesting concepts are still hypothetical.

Respiratory Symptoms. Pharyngitis, tonsillitis, sinusitis and laryngitis occur frequently before the onset of an acute episode of rheumatic fever. A specific rheumatic nature has sometimes been ascribed to these upper respiratory infections. The characteristic rheumatic inflammation including Aschoff bodies has been observed in the peritonsillar fibrous tissue and adjacent musculatures. Hoarseness and respiratory distress may be due to pressure on the recurrent laryngeal nerve, inflammation of the crico-arytenoid joints or large lymph nodes.

Pleurisy, either fibrinous or with effusion, is observed clinically in 5 to 15 per cent and post mortem in more than 50 per cent of cases.[92] Pleurisy is generally associated with pulmonary and cardiac disease including pericarditis.[105] Pleural effusion may be unilateral or bilateral and occurs more frequently on the left side, probably due to the proximity of the left pleura to the pericardium. Paul,[92] however, found it more often on the right side at post mortem examination, and even in the absence of gross pericarditis. Microscopic lesions may have been present in the pericardium in such cases. As indicated by Bezançon and Weil[11] the pleural lesions may arise by extension from cortical pulmonary disease (cortico-pleurite) as well as from the pericardium.

The onset of pleurisy is associated with sharp pain over the chest, and intensified by inspiration or motion of the chest wall. Pain may radiate to the abdomen and produce a picture resembling an acute abdominal complication. A pleural friction rub may be present or only diminished breath sounds and a few subcrepitant râles. After a few days the pain usually disappears and there are evidences of fluid at the bases of the lungs posteriorly. The physical signs are often confusing because of the frequent association of pulmonary lesions and pericardial effusion. The pleural effusion is rarely of sufficient size to

produce significant respiratory distress or require tapping. If routine anteroposterior and oblique roentgenologic views of the chest are taken, a rheumatic pleurisy may be demonstrated in a high percentage of cases.[122] The interlobar fissures appear thickened.

The specific rheumatic nature of the pleurisy was first mentioned by Stoll and accepted by numerous French and English observers.[92] Clinically a resemblance to rheumatic arthritis has been seen in the rapid development and subsidence of the pleurisy. Mosler[86] pointed out that the pleurisy was merely one of the evidences of the tendency of rheumatic fever to affect serous membranes, and spoke of polyserositis rheumatica.

Pathologically the rheumatic nature of the pleurisy has been supported by the observation of inflammatory lesions in the subendothelial connective tissue consisting of collagen swelling and degeneration, edema, infiltration with lymphocytes, leukocytes and giant cells and scar formation; but Aschoff bodies have not been described.

The pleural exudate[101] is serofibrinous, appears turbid and straw-colored and on standing one hour separates out a clear serous fluid and a coagulum containing a variety of cells. French authors lay special stress on the characteristic nature of the cellular exudate which is composed of a predominance of polymorphonuclear leukocytes over lymphocytes and especially of endothelial cells occurring in large numbers both singly and in sheets. The effusion is an exudate. It may be hemorrhagic. In many of the cases with sanguineous effusion, it is probable that the pleural exudate appeared in connection with pulmonary infarction. Rapid and complete resorption of the effusion is the rule, but occasionally resorption is delayed (pleurésie fixé) and adhesions may develop.

Pneumonia in Rheumatic Fever. The occurrence of a *specific rheumatic* pneumonia has been the subject of considerable confusion and disagreement (p. 710). Latham[70] and Fuller[40] first emphasized the occurrence of a rheumatic pneumonia, physical signs of which they observed clinically in about 15 per cent of their cases of rheumatic fever. Griffith et al.[46] recently reported the clinical observation of pneumonitis in 11.3 per cent of 1046 patients with prolonged rheumatic fever. The pathologic findings in the lung have been described above (p. 710).

The reported clinical features of "rheumatic pneumonia" are even less consistent than the pathologic findings. Rabinowitz[100] emphasized the presence of atypical bilateral, migrating signs of consolidation without the usual symptoms of pneumonia, i.e., cough was slight or absent, sputum scanty and fever of low grade. This corresponds to the "congestion pulmonaire latente" of Bernheim.[10] Seldin and his associates[118] on the other hand characterized rheumatic pneumonia by the abrupt onset of profound breathlessness and orthopnea, hacking cough, scanty sputum which is occasionally blood-streaked, pleuritic pain and frequent cyanosis. These symptoms are associated with high fever, leukocytosis and bilateral multilobar, nonsegmental infiltrations similar to the shadows of pulmonary edema. Physical signs are relatively few. According to Griffith and associates,[46] rheumatic pneumonia is characterized by dyspnea and tachycardia, fever, pleuritic pain, cough and malaise, shifting areas of dullness, diminished breath sounds and fine râles and transient pleural effusions. The roentgen ray appearance is similar to that of primary atypical pneumonia.

It is very probable that the reported symptoms, physical and roentgen ray signs associated with so-called rheumatic pneumonia do not have a unitary pathologic basis, but result from pulmonary infarction, left-sided heart failure with or without transient pulmonary edema, as well as an atypical pneumonia which may or may not be characteristic of rheumatic fever. In particular the occurrence of pulmonary infarcts, due to emboli from thrombi in the leg veins or right atrium, is often overlooked. These may be characterized by sudden dyspnea, tachycardia, fever and leukocytosis, with or without pleural effusion, while the better known chest pain and hemoptysis are absent or overshadowed. Heart failure may be precipitated or intensified by such emboli and in particular, transient pulmonary edema may ensue. Persistent rheumatic activity or recrudescence is often diagnosed when unrecognized pulmonary infarction occurs.

Corresponding to these mixed pathologic lesions roentgenologic examination of the lung may disclose a variety of pictures[117] including (1) pulmonary congestion with increased vascular markings due to early left heart failure, (2) acute pulmonary edema with central densities radiating from the hilar regions, (3) pulmonary infarcts often indistinguishable from areas of consolidation or atelectasis, (4) pleural effusion which may be due to rheumatic inflammation or to pulmonary infarction, (5) "rheumatic pneumonitis" characterized by large, small or confluent densities indistinguishable from atypical pneumonia, atelectasis or infarction. In cases of prolonged rheumatic fever and rheumatic heart disease there may be roentgen ray evidence of chronic pulmonary edema, pulmonary fibrosis and pleural thickening.

Gastrointestinal and Abdominal Symptoms. Constipation, diarrhea and abdominal distention have been noted as frequent complaints in children prior to development of definite rheumatic fever ("pre-rheumatic children"). They are probably coincidental symptoms unrelated to rheumatic fever. Libman[76] noted two cases of rheumatic fever associated from the onset with ulcerative colitis. But diarrhea is not an intrinsic feature or a common symptom in rheumatic fever. Vomiting and rarely diarrhea, when present, may be due to the administration of salicylates or digitalis or to advanced heart failure.

Abdominal pain is a common and serious symptom. When it arises in the course of a well developed attack of rheumatic fever, it is not likely to be misinterpreted. But not infrequently it precedes any definite rheumatic symptoms and may simulate an acute abdominal complication.[2] There may be abdominal tenderness, nausea and vomiting. I have occasionally observed such patients mistakenly operated upon for acute appendicitis. Abdominal pain may arise by several mechanisms. Most commonly it is referred from the chest, where there is a pericarditis or pleurisy. There may be a polyserositis including a perihepatitis as well as pleuropericarditis. In right heart failure, pain, abdominal tenderness and vomiting may be due to a congested liver. I have reported two cases in which an appendectomy was performed because of abdominal pain and tenderness due to a diffuse necrotizing arteritis involving the appendiceal as well as other vessels.[36] Pain may result from a serous peritonitis.[142, 9] Rhea[103] recently observed such a case in which he reported finding a rheumatic inflammation, but his microphotographs do not appear to show specific lesions. A rheumatic myositis of the right rectus muscle has also been postulated.[102]

Renal Symptoms. Intermittent slight *albuminuria* is common in the presence

of fever. According to Goldring and Wyckoff,[42] there is often a mild focal nephritis, as indicated by abnormal urinary protein, casts, leukocytes and erythrocytes determined by the Addis sediment count.

Acute diffuse glomerulonephritis is very uncommon, occurring in less than 1 per cent of cases of rheumatic fever.[105, 110] Baehr and Schifrin[5] discovered only 2 cases of acute diffuse glomerulonephritis among 235 necropsied cases of rheumatic heart disease. I have seen two anatomically proven cases of active rheumatic heart disease and acute glomerulonephritis, and others have occasionally reported the association.[77] But it is more important to emphasize the rarity of this combination, and the presence of definite acute diffuse glomerulonephritis should cast suspicion on the diagnosis of acute rheumatic fever. Often in such cases, the clinical picture is due neither to rheumatic fever nor to glomerulonephritis but to periarteritis nodosa, Libman-Sacks disease (with or without lupus erythematosus), or to subacute bacterial endocarditis. These diagnoses probably may be applied to most of the reported cases of renal vascular lesions or "nephritis" in acute rheumatic fever.[110, 57]

Chronic glomerulonephritis is not infrequently combined with rheumatic heart disease, which is usually inactive. But there is no reason to believe that the combination is more common than is to be anticipated from the incidence of the two diseases.

Malignant sclerosis is occasionally encountered in rheumatic fever. Fahr[32] has ascribed considerable significance to the role of rheumatic infection in the production of malignant sclerosis. I have reported an anatomically proven case of the latter in association with active rheumatic fever, periarteritis nodosa and uremia. But in such cases the malignant sclerosis must be ascribed to the vascular lesions of periarteritis nodosa rather than to the rheumatic infection, since we know that there is a frequent association of the first two diseases independent of rheumatic fever.

Renal infarcts with or without hematuria may be the result of emboli to the kidney from thrombi in the left auricular appendage. In the absence of auricular fibrillation or in the presence of unexplained fever renal infarction should suggest bacterial endocarditis and not rheumatic activity or bland embolization. *Azotemia* of moderate degree and without uremic symptoms is observed commonly when cardiac failure is present. *Hematuria* or *hemoglobinuria* may occur very rarely when there is renal infarction. They are more suggestive of bacterial endocarditis than of rheumatic fever and heart disease.

Graves' Disease and Thyroiditis. Graves' disease has been recorded as occurring in association with chorea and with valvular heart disease.[113] The development of an acute thyroiditis as a manifestation of rheumatic fever has been stressed particularly by Vincent,[131] who elicited a history of rheumatic fever in 43 per cent of his cases of Graves' disease. His criteria for diagnosis are subject to criticism. Occasionally in the course of rheumatic fever, the patient develops severe pain, swelling and redness in the region of the thyroid gland. Suppuration does not occur. The inflammation generally subsides uneventfully in forty-eight hours. Vincent[132] has reported a case of acute "rheumatic thyroiditis" followed by atrophy of the gland and scleroderma. Occasionally there is a permanent increase in the size of the thyroid gland. Even in the absence of thyroiditis, an acute diffuse scleroderma has been observed in a young girl who died four weeks after the onset of acute rheumatic fever.[78]

I have observed several cases in which symptoms of Graves' disease de-

veloped in the course of rheumatic fever with or without signs of thyroid inflammation. I have also observed many cases of rheumatic mitral stenosis associated with Graves' disease. Sergent[119] reported a case in which every attack of rheumatic fever was accompanied by hyperthyroid symptoms, the patient finally showing a complete Graves' syndrome. Despite these varied observations, it is improbable that either thyroiditis or hyperthyroidism is a specific consequence of rheumatic fever.

Diseases of Blood Vessels. The diffuse vascular lesions described by Klotz[69] and by von Glahn and Pappenheimer[133] are clinically insignificant. While it is possible that the lesions of the aorta and pulmonary artery may give rise to clinical symptoms, the numerous reports of rheumatic aneurysm, particularly in the French literature, are generally instances in which the etiology is probably syphilis or bacterial endocarditis. However, some instances of angina pectoris in rheumatic fever may be due to rheumatic lesions in the aorta or in the innominate or coronary arteries. The possible etiologic role of rheumatic fever in coronary arteriosclerosis has been discussed (p. 403). Libman[76] pointed out that sometimes there is local tenderness over the carotid and innominate arteries due to arteritis. I have reported with Gross[36] four anatomically proven cases of active rheumatic heart disease with diffuse necrotizing arteritis. In these cases, the vascular lesions were sufficiently extensive to produce symptoms which dominated the clinical picture, including orchitis, and abdominal pain which induced surgical intervention.

Epistaxis has been repeatedly noted as a manifestation of rheumatic children, especially during rheumatic activity or before a recurrence.[76, 72, 22] It has been attributed to an increased capillary permeability and fragility and a tendency to low blood platelets in rheumatic fever.[85, 136] I believe the frequency and significance of epistaxis as a specific rheumatic symptom has been exaggerated.

Phlebitis is rare. A critical study of rheumatic phlebitis was presented by Schmitt.[115] I am unconvinced that the phlebitis is a rheumatic manifestation.

AFFECTIONS OF THE EYE. Iritis, episcleritis and occasionally phlyctenular conjunctivitis have been reported as manifestations of rheumatic fever. Optic neuritis occurs rarely. The specific relationship of these symptoms to rheumatic fever is unproven.[109] Many of the reported cases were undoubtedly instances of gonorrheal disease with arthritis or of subacute bacterial endocarditis, not rheumatic fever. Or they may have represented ileitis or ulcerative colitis.

LYMPHADENITIS. Swelling of the tonsillar lymph nodes is common. Swelling of the tracheobronchial nodes may occur and produce a hoarse dry cough. Transient generalized adenopathy has been reported. Differentiation from Still's disease is important, and the latter appears to be a more likely diagnosis in some of the reported cases, e.g., that of Barlow.[6]

Orchitis occasionally occurs in rheumatic fever. Its presence should lead to a suspicion of an associated necrotizing arteritis.[36]

Osteitis and periostitis are other complications whose rheumatic etiology is in dispute. It seems probable that the cases reported as rheumatic were due to syphilis or osteomalacia.

Blood and Urine. A *leukocytosis* is common in active rheumatic fever[128, 141, 59] and is a significant index of active infection. The white blood count is generally between 10,000 and 16,000 per cubic millimeter. Occasionally it may exceed 20,000 or it may lie within normal limits. Salicylate therapy

may lower the white blood count as well as the temperature. A leukocytosis may persist into the afebrile stage. It then becomes a more delicate index of rheumatic activity than the temperature. On the other hand rheumatic activity may persist even after the leukocyte count has fallen to normal. An absolute and relative increase in polymorphonuclear leukocytes accounts for the leukocytosis. There is a shift to the left in the number of nonfilamented polymorphs by the Schilling count.[125] The remaining white cells are normal, but in chorea there may be an eosinophilia.[8]

Anemia is a common feature of active rheumatic fever.[55] The hemoglobin may fall as low as 6 or 7 gm. per 100 cc. although it usually lies between 8 and 12 gm. and gradually rises as active "infection" subsides. The red blood cell count ranges between 3 and 4 million per cubic millimeter. The anemia is of the microcytic type.[50]

That the *rate of sedimentation of red blood cells is increased* in rheumatic fever was observed by Kahlmeter.[61] In one hour, the column of plasma by Westergren's method may reach 100 to 120 mm. as compared with 1 to 7 mm. for normal women and 1 to 11 mm. for men. With subsidence of rheumatic activity, the rate of sedimentation reverts to normal. Of great significance, however, is the observation that the sedimentation rate may remain rapid for some time after the temperature and white count become normal.[31, 94, 24, 125, 136, 51] Thus it appears to be an especially sensitive index of persistent rheumatic infection. In the presence of congestive heart failure, occasionally the sedimentation rate may fall to normal even in the presence of active infection.[93] In cases of chorea without associated manifestations of rheumatic fever or carditis, the sedimentation time is normal.[21, 23]

The *fibrinogen* content of the blood plasma was reported as being elevated by Bezançon and Weil,[11] who use this as a sign of persistent activity. It appears to parallel the sedimentation rate.[31]

An *abnormal (shortened) coagulation band in the Weltmann reaction* is associated with rheumatic activity and was considered by Scherlis and Levy[114] to be at least as significant in this respect as the rapid sedimentation rate.

The *formol-gel* test may be positive, but this is only irregularly found with active rheumatic fever.[18] The positive formol-gel test corresponds with the tendency to high serum globulin in rheumatic fever.[30]

Blood cultures are generally negative. In about 5 per cent of cases an occasional positive blood culture is obtained, usually of the Streptococcus viridans (alpha) or anhemolyticus (gamma). But these organisms are almost invariably grown only in fluid media, a point which indicates that the organisms are few in number. On the other hand, positive cultures of these organisms in subacute bacterial endocarditis are obtained both on solid and fluid media.

The *urine* contains a trace of *albumin* in the febrile state and in the presence of congestive heart failure.

ELECTROCARDIOGRAPHIC CHANGES

Electrocardiographic abnormalities are almost always present at some time during the course of active rheumatic fever.[26, 108, 75] These disturbances are only occasionally recognizable clinically. Even when clinical arrhythmias are present, their accurate interpretation generally requires electrocardiographic study. Furthermore, since the arrhythmias are characteristically evanescent, the frequency with which they are discovered is proportional to the frequency

of cardiac and electrocardiographic examination. Electrocardiographic changes were found in about 40 per cent of the cases of chorea studied by Heffer.[54]

The importance of electrocardiographic changes in rheumatic fever lies in the facts that: (1) they suggest the occurrence of cardiac damage in almost every case of that disease; (2) they serve as an important, sometimes as the only, sign of cardiac damage. As a corollary, the electrocardiograph may be used to determine the persistence of cardiac infection in a known rheumatic cardiac. Thus Shapiro[120] demonstrated the persistence of active infection in 65 per cent of children with supposedly quiescent rheumatic heart disease, by taking successive electrocardiograms which revealed abnormal or changing curves.

Three types of electrocardiographic abnormalities are encountered in rheumatic fever: (1) impaired atrioventricular conduction, (2) abnormalities in the QRST complex and more rarely in the P wave and (3) changes in cardiac rate and rhythm.

1. Impaired Atrioventricular Conduction. (a) *Prolongation of the P-R interval* is the most frequent significant electrocardiographic abnormality in rheumatic fever. The P-R interval exceeds 0.20 second, occasionally lies between 0.3 and 0.4, and even longer P-R intervals have been observed. Prolonged P-R interval has been noted in 25 to 95 per cent of active cases, the higher incidence being obtained with frequent and numerous electrocardiographic examinations.[26, 108, 75, 80, 87] A prolonged P-R interval may be encountered in a great variety of infections and infectious diseases (p. 834), but not as regularly as in rheumatic fever. As a rule, the prolongation of the P-R interval is a transient disturbance, but occasionally it persists for weeks or months.

The prolongation of the P-R interval may be due directly to reversible rheumatic inflammation of the a-v node and bundle,[47] but it has also been attributed to vagal stimulation.[14, 67] Thus carotid sinus pressure and prostigmine may increase the prolongation of the P-R interval,[48] while atropine reduces the P-R interval in rheumatic fever.[104] These observations, however, do not exclude the possibility that the effect of rheumatic fever is on the conduction system directly, while the augmenting or inhibitory effect of the drugs is by way of the vagus nerve. Furthermore, rheumatic lesions may render the a-v conduction system abnormally sensitive to vagal stimulation.

(b) More severe grades of *heart block* are occasionally observed, with 2:1, 3:1 or 3:2 block. Dropped beats and Wenckebach periods have been noted. Complete heart block is very uncommon, but it may be the earliest manifestation of rheumatic heart disease and may occur in the absence of fever.[138, 137] Rarely there is an Adams-Stokes syndrome.[33, 124] Almost always heart block disappears when the infection subsides, but occasionally it persists permanently. Bundle branch block is observed occasionally. Interference dissociation (p. 246) may be an early finding[123] and occurred in 18 of 1000 cases of rheumatic fever studied by Rosenberg.[106]

2. Abnormalities in QRST and in P Waves. The frequency of QRS, ST and T wave changes in rheumatic fever was emphasized by Cohn and Swift[26] and by Rothschild et al.[107] Master and Jaffe[80] reported finding ST and T wave changes in at least 80 per cent of their cases, and Blackman and Hamilton[12] in 61 per cent.

(a) *Deviations in R-T or S-T interval.* There may be an elevation or depression of RST transition. Most often there is an R-T elevation in two or more leads, due to rheumatic pericarditis.

(b) *T wave alterations* consist of inversion, especially in leads I and II. Similar T wave inversions and R-T abnormalities are observed also or only in the precordial leads.[73, 4, 35] The T waves may also be diphasic or of low voltage. Inverted T waves in some cases are due to pericarditis with effusion.

(c) Changes in the QRS complex consist of lowering of the voltage of the major deflection or occasionally of notching, slurring and widening due to delayed intraventricular conduction or bundle branch block.

(d) A *prolongation of the Q-T interval,* both absolute and relative to diastole, has been stressed as a universal finding in active rheumatic carditis by Taran and Szilagyi.[129] They found the Q-T interval to be a measure of the severity of the carditis, and valuable both for following progress and discovering persistent activity, even when all other laboratory criteria are normal. The value of measuring the Q-T interval and its clinical significance are still moot questions.

(e) P wave inversion or flattening has been described as evidence of rheumatic activity.[34, 111]

3. Changes in Cardiac Rate or Rhythm. (a) *Sinus tachycardia* is almost always found in the presence of fever and often for a variable period after the fever is gone. Occasionally there are attacks of paroxysmal tachycardia. Bradycardia is rarely found in the presence of severe heart block, but more commonly sinus bradycardia occurs during convalescence.[91] Sinus arrhythmia is common.

(b) Premature auricular or ventricular contraction occurs occasionally, but most often in patients with previous valvular deformity.

(c) Auricular fibrillation and flutter have been observed; they are usually paroxysmal but the former may persist.

(d) Nodal rhythm, sinoauricular block and wandering pacemaker have been documented rarely in reported cases of rheumatic fever. The role of digitalis in their production must be considered (p. 190).

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33

RHEUMATIC FEVER

Diagnosis, Differential Diagnosis, Prognosis and Treatment

DIAGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

The diagnosis of rheumatic fever and rheumatic heart disease[71, 54] involves the recognition of (1) active rheumatic fever with or without cardiac involvement, and (2) rheumatic heart disease in patients without rheumatic activity.

The Presence of Active Rheumatic Disease

It is important to reemphasize that there is no specific test for rheumatic fever and that diagnosis of this disease is often necessarily based on nonspecific clinical and laboratory abnormalities which are similar to those caused by other diseases. In order to establish relatively uniform statistical data and to avoid the serious implications, restrictions and psychologic disturbances that accompany a diagnosis of rheumatic fever, it seems desirable to satisfy strict criteria before this diagnosis is justified. The frequent discovery of rheumatic heart disease on physical or postmortem examination in subjects who presented no history of rheumatic fever suggests that the latter is often overlooked or that it often occurs in a subclinical unrecognizable form. However, this does not justify the overemphasis in recent years on minor and nonspecific abnormalities as an adequate basis for the diagnosis of rheumatic fever.

Rheumatic fever may be indicated by cardiac or extracardiac symptoms. Even when there are only extracardiac symptoms, the likelihood of cardiac involvement in the first or subsequent attacks of rheumatic fever is so great that the patient must immediately be considered as having actual, possible or potential heart disease. Active rheumatic infection should be recognized when it occurs as a first attack, when it flares up during the course of convalescence or shortly thereafter, and when it appears many years later in a rheumatic cardiac who has long been asymptomatic.

The diagnosis of rheumatic fever is relatively simple when several of the more characteristic features develop simultaneously or in rapid sequence. Difficulty arises when there are only nonspecific *general* symptoms such as fever, tachycardia, etc., or when there is only a single localizing symptom such as joint pains. Certain individual symptoms have greater diagnostic significance than others and are practically pathognomonic. Other symptoms, of less significance individually, assume importance when they appear jointly with additional rheumatic manifestations.

The most important feature of rheumatic fever and the most definitely diagnostic is cardiac involvement. *The combination of fever with congestive heart failure, rapidly progressive cardiac enlargement or pericarditis* in a child or young adult almost always denotes active rheumatic fever. Congenital heart disease, suppurative pericarditis and subacute bacterial endocarditis are relatively easy to differentiate. As a rule, careful observation will disclose confirmatory findings such as arthritis, subcutaneous nodules or distinctive erythemas.

Electrocardiographic abnormalities, especially a pronounced prolongation of the P-R interval, are in themselves or in combination with fever insufficient to justify a diagnosis of rheumatic fever or rheumatic heart disease, since these abnormalities occur with many other infections and infectious diseases[25] (Chapter 36). However, they may denote cardiac involvement or continued activity in cases in which the diagnosis of rheumatic fever or rheumatic heart disease is justified on other grounds.

Sydenham's chorea is suggestive of rheumatic fever even when it occurs as an isolated symptom. But when it occurs in association with fever, arthritis, or other symptoms of rheumatic fever which in themselves are nonspecific, a definite diagnosis of rheumatic fever is justified.

Subcutaneous nodules and *erythema marginatum* are in themselves diagnostic of rheumatic fever, but there are occasional errors in interpretation of these subcutaneous and cutaneous lesions. As a rule the diagnosis can be made with certainty because careful observation will disclose simultaneous fever, joint pains, carditis or other rheumatic phenomena.

Fever and arthritis are characteristic of rheumatic fever, but unfortunately too nonspecific in etiology to permit a definite diagnosis. A distinction should be made between muscle and tendon "growing pains" which are nonrheumatic and definite joint pains which may or may not denote rheumatic fever.[131] Although atypical arthralgias or arthritis may signify rheumatic fever, the diagnosis is more likely if there is a typical polyarthritis with inflammatory changes migrating to new joints as they subside in others. A striking and rapid amelioration of pain, inflammation and fever should follow adequate doses of salicylates, but this may occur less frequently in other types of arthritis. The history of a streptococcus A infection of the nose or throat or of scarlet fever one to four weeks preceding the arthritis, and the association of distinctive electrocardiographic abnormalities (p. 737), enhance the probability of rheumatic fever.[116, 158]

A variety of minor symptoms occur frequently in rheumatic fever but appear also in so many other conditions that they have limited diagnostic value. They may serve to call attention to the possibility of rheumatic fever when several of them occur in combination, in children or young adults. These minor symptoms include low grade fever with malnutrition, pallor, tachycardia, recurrent sore throat, frequent epistaxis and abdominal pain. However, the diagnosis is not justified until careful observation discloses more specific symptoms such as carditis, arthritis, etc.

Under special circumstances nonspecific symptoms may assume increased diagnostic importance. In the patient with a *definite* previous attack of rheumatic fever, especially a recent one, a diagnosis of rheumatic recurrence may be made on less rigid criteria than are required to diagnose the first attack. In epidemics of definite rheumatic fever, similar diagnostic latitude is permissible.

But even under such circumstances only *probable* rheumatic fever should be diagnosed unless the more rigid criteria, mentioned above, can be satisfied.

Signs of Persistent Rheumatic Activity. When typical clinical signs of rheumatic "infection" disappear, persistent rheumatic activity may be denoted by various clinical or laboratory findings.[150] These include:

Fever. A low grade fever may persist for many weeks. This may be discovered only by rectal thermometry performed several times daily. On the other hand, good clinical judgment often justifies disregarding prolonged low grade elevations in temperature in the absence of other significant manifestations. Some normal children have a temperature slightly beyond the usual normal range.[153] Disappearance of fever is suggestive of subsidence of activity, provided that salicylates or similar antirheumatic drugs have been discontinued. On the other hand, it is generally well known that rheumatic activity often persists for weeks after the temperature has fallen to normal and that such rheumatic activity may be disclosed by other clinical or laboratory findings.

Tachycardia. A rapid cardiac and pulse rate persists, as a rule, even after the temperature is normal. It usually denotes rheumatic activity and often cardiac impairment. However, occasionally a rapid pulse rate during convalescence slows if the patient is gradually permitted to resume activity. In such instances the tachycardia is due to a generally poor physical fitness (lack of training) rather than to specific myocardial disease. Not infrequently a persistent tachycardia is of "nervous" or psychic origin and the sleeping pulse rate is found to be normal.[144, 126]

Leukocytosis. Although the white blood count may be normal, there is usually a leukocytosis in the presence of persistent rheumatic activity. Special emphasis is placed on a polymorphonuclear shift to the left in the Schilling hemogram. Often leukocytosis in acute rheumatic fever persists for days or weeks after the disappearance of fever.

Increased Sedimentation Rate of Erythrocytes. This is generally regarded as the most sensitive test of persistent rheumatic inflammation. Accuracy in performance of the test is essential if this is to be used as a decisive factor in determining the presence of persistent rheumatic activity.

Persistent weight loss or failure to gain is associated with active rheumatic fever. Subsidence of activity usually is followed by restoration of appetite and progressive gain in weight. Increased weight due to edema of heart failure must be excluded.

Electrocardiographic Abnormalities. Distinct prolongation of the P-R interval, and especially continued electrocardiographic changes in successive records, are indicative of persistent rheumatic infection. A prolonged Q-T interval may also be significant of rheumatic activity (p. 739).

Clinical observations must be carefully evaluated in any determination of persistent rheumatic activity. There must be no evidence of cardiac, arthritic or other manifestations of rheumatic fever and the general appearance and behavior of the patient should signify the absence of active infection. In children and young adults with rheumatic cardiovalvular disease, progressive cardiac enlargement or the development or persistence of heart failure usually denotes persistent rheumatic infection whether or not there are any of the above-mentioned clinical or laboratory signs. *The presence of minor rheumatic manifestations* should suggest persistence of activity even though such minor phe-

nomena would not be sufficient to diagnose the actual attack of rheumatic fever.

In fact *it is important to emphasize that the clinical and laboratory phenomena which denote persistent rheumatic activity are to be distinguished from those manifestations which are originally diagnostic of the disease.* Thus unexplained low grade fever, leukocytosis and an increased sedimentation rate in a child do not add up to rheumatic fever in the absence of some more diagnostic feature. Even arthritis, fever and a rapid sedimentation rate is not necessarily rheumatic fever.

In my experience many a child and young adult with unexplained low-grade fever has been long invalided and unfairly tagged with the diagnosis of rheumatic fever when the sedimentation time was found to be rapid—as if the unexplained fever suggested and the rapid sedimentation rate confirmed the diagnosis. A functional systolic murmur added to these two features frequently completes the unfortunate triad which leads to the unwarranted sentence of rheumatic heart disease. Not infrequently determination of the temperature after the child has been at complete rest for half an hour dissipates the "fever," determination of the sedimentation rate by an expert slows the rate of fall of the erythrocytes to normal, and listening to the heart in full inspiration eliminates the murmur.

Cardiac Involvement During Acute Rheumatic Fever. Every attack of rheumatic fever involves the concomitant diagnosis of potential or possible rheumatic heart disease. A definite diagnosis of rheumatic heart disease during the attack must be based on symptoms and signs of cardiac failure, pericarditis, definite cardiac enlargement under observation or an unequivocal diastolic murmur. Diastolic gallop rhythm, distinct prolongation of the P-R interval in the electrocardiogram, disproportionate and protracted tachycardia are suggestive but not definite evidences of organic rheumatic cardiac disease. A *loud* systolic murmur with radiation to the axilla, which is constant despite exercise or changes in position or respiratory phase, and which persists for more than six months after subsidence of the acute attack, also denotes organic heart disease.[108, 80] However, the variability and regression of physical signs in organic rheumatic heart disease in children have been stressed by several observers.[18, 164]

The Presence of Rheumatic Heart Disease in Patients without Active Rheumatic Fever

This is generally the problem encountered in adult patients who often appear healthy and are unaware of any cardiac disease. The physician must determine whether or not there is organic heart disease, and, if present, whether such heart disease is of rheumatic etiology. He must also consider the possibility that there is active rheumatic infection in the heart even though none of the common extracardiac symptoms are present.

The existence of cardiac disease is usually clear when there are definite symptoms of heart failure, or of pronounced cardiac enlargement. In the absence of such symptoms and signs, the diagnosis is dependent on physical and roentgen ray examination and electrocardiography. In rheumatic heart disease the diagnosis usually is based on recognition of the evidences of valvular heart disease[61] (Chapters 26–29). These evidences include characteristic murmurs and distinctive forms of cardiac enlargement as visualized by roentgen ray.

When the presence of organic heart disease has been determined, its rheu-

matic etiology may be surmised if there is a definite history of rheumatic fever. This assumption is especially probable if there is also a history of a cardiac murmur which persisted after the rheumatic attack. However, more than half of young adults with rheumatic heart disease present no history of rheumatic fever.[85]

The character of the valvular lesion is often suggestive of the rheumatic etiology. The combination of aortic insufficiency and mitral stenosis, or mitral stenosis alone, almost always denotes rheumatic cardiovalvular disease, although rarely mitral stenosis may be due to an auricular tumor. Aortic stenosis, as a rule, signifies rheumatic heart disease, although occasionally it may represent a congenital subaortic stenosis or rarely it may be due to nonrheumatic calcification. Aortic insufficiency alone may be rheumatic or syphilitic; the differential diagnosis is discussed elsewhere (p. 598). Organic systolic murmurs may represent rheumatic mitral insufficiency or aortic stenosis, but must be differentiated from functional murmurs (p. 570) and from congenital cardiovascular lesions (p. 682).

Sometimes a rheumatic mitral stenosis is first suggested by left atrial enlargement on fluoroscopic or roentgenographic examination, by unexplained hemoptysis, auricular fibrillation, cerebral embolization or heart failure. Similarly aortic insufficiency may be first suggested by the abnormal configuration of the heart or by abnormal circulatory dynamics associated with this lesion (p. 595).

That the rheumatic heart disease which the physician has diagnosed is *inactive* depends on negative data, particularly the exclusion of all of the symptoms presented under active rheumatic fever. The cardiac disease may remain inactive even in the presence of recurrent extracardiac rheumatic symptoms, but this is the exception rather than the rule. On the other hand, active rheumatic infection may be present in the heart without clinical manifestations anywhere else. Cardiac failure with or without low-grade fever may be the only evidence. Activity in the heart may also be indicated by changes in physical signs, x-ray or electrocardiographic alterations or diminished circulatory efficiency.

However, every febrile episode in a known rheumatic cardiac should not be interpreted as an activated rheumatic carditis even though this possibility must be considered. In the absence of an obvious cause of fever of more than one week's duration, the possibility of subacute bacterial endocarditis should be carefully investigated. When fever and heart failure occur in the child or young adult with rheumatic heart disease, active rheumatic carditis is usually present. But in older adults pulmonary embolism is probably the most common cause of fever in combination with congestive heart failure.

DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER

Since the discovery of rheumatic heart disease often depends on the recognition of noncardiac evidences of rheumatic fever, it is important to consider the differential diagnosis of the general disease, as well as of the cardiac lesion.[58, 71, 54] Problems in the differential diagnosis of rheumatic fever arise when there are only general, nonspecific symptoms of an obscure infection or when the local symptoms present are confined to a single organ system.

1. *Subacute Bacterial Endocarditis.* This offers one of the most frequent problems in differential diagnosis in adults with compensated rheumatic heart

disease. The patient is recognized as having rheumatic valvular heart disease, but the physician must decide whether the fever and other symptoms present are due to activation of a rheumatic infection or to a complicating subacute bacterial endocarditis or to both. The differential diagnosis is discussed on pp. 793-4.

2. *"Grippe," nasopharyngitis or other infections of the respiratory tract* may be erroneously diagnosed as rheumatic fever or vice versa. Following a mild upper respiratory infection in a child there may be persistent low grade fever and indefinite muscle or juxta-articular pain. These are insufficient to diagnose rheumatic fever, even when the sedimentation rate is rapid. However, awareness of the possibility of rheumatic fever may lead to careful observation and eventual discovery of cardiac involvement, arthritis, nodules or characteristic rheumatic dermatoses. A so-called "grippe" or "pneumonia" followed several months later by definite cardiovalvular disease may have to be reinterpreted as an attack of rheumatic fever.

3. *Pulmonary tuberculosis* may be considered when the rheumatic child presents fever, anorexia, pallor and malnutrition. The occasional presence of arthritis and of pleural effusions in tuberculosis may add to the difficulty of differential diagnosis. Roentgenographic examination of the chest, tuberculin tests and sputum examinations decide the problem. I have several times observed a tuberculous arthritis in a child treated as rheumatic fever until expert roentgenologic examination of the joint suggested the correct diagnosis.

4. *Rheumatoid Arthritis in Adults and Still's Disease in Children.* Rheumatoid arthritis is distinguished essentially by the absence of cardiac involvement. Electrocardiographic abnormalities, which are the rule in rheumatic fever, are absent in rheumatoid arthritis.[97] In rheumatoid arthritis the small joints are more frequently and more severely affected. They may assume a fusiform or spindle-shaped appearance. Deformity and ankylosis are common but may develop only in advanced stages. The rapidly migrating character of the rheumatic polyarthritis is rarely observed in rheumatoid arthritis and salicylates do not produce as dramatic a relief of pain, disappearance of swelling and effusion, and restoration of normal temperature. In the absence of cardiac manifestations, of other distinctive features, or of a previous history of rheumatic fever, the diagnosis of rheumatic fever on the basis of fever and arthritis alone is always subject to question.

Still's disease in children is differentiated by the presence of rheumatoid arthritis and by the association of diffuse adenopathy and splenomegaly.

5. *Osteomyelitis* may simulate rheumatic fever because of pain near the end of an extremity and the presence of fever. Careful localization of the pain and tenderness and later roentgenologic examination suggest the proper diagnosis.

6. *Leukemia and Cooley's Anemia.* I have seen cases of these diseases erroneously diagnosed as rheumatic fever because of the combination of joint pains, pallor and anemia, and a cardiac murmur. Fever may also be present. Roentgen ray examination discloses characteristic bony lesions, and abnormal cells are found in the blood.[133]

7. *Sickle-cell anemia* may likewise be characterized by joint pains, anemia, abdominal pain and a cardiac murmur. Its differential diagnosis is discussed on p. 974.

8. *Poliomyelitis* may be confused with rheumatic fever but meningeal signs,

spinal fluid abnormalities and paralyses characterize the former. Pains in the muscles should be distinguished from the joint pains of rheumatic fever.

9. *Schönlein's disease* (peliosis rheumatica) is characterized by joint pains but can be distinguished by extensive purpuric lesions near the joints and by the absence of cardiac or other features of rheumatic fever.

10. *Scurvy*. Pain and swelling may seem to be localized to the joints and may suggest rheumatic fever. The disease occurs mostly during infancy at which time rheumatic fever is rare. A history of dietary deficiency, ecchymoses (especially at the lower end of the femur), swelling and sponginess of the gums, characteristic roentgen ray appearance of the bones and therapeutic response to vitamin C are features of scurvy.

11. *Hemophilia* is associated with hemorrhage into the joints with consequent pain and swelling. Its occurrence only in males and the prolonged clotting time differentiate it from rheumatic fever.

12. *Congenital syphilis* may simulate rheumatic fever when there is pain and swelling near the joints due to epiphysitis. A positive Wassermann test and distinctive roentgenologic findings in the bones are diagnostic. By similar means it is possible to distinguish the rapidly developing, usually painless joint swellings occurring in late congenital or acquired syphilis (Charcot joints).

13. *Disseminated lupus erythematosus* is often diagnosed as rheumatic fever because of the frequent combination of fever and arthralgias or arthritis at the onset, and the occasional presence of a pericardial rub. It is distinguished by the appearance of the characteristic butterfly rash on the face and bridge of the nose, by lesions on fingers and palms, by leukopenia and by an almost exclusive occurrence in young adult females.

14. *Gonococcemia and Gonorrheal Arthritis*.[130a] The history of urethral discharge, the tendency to monarticular involvement and the absence of striking response to salicylates aid in distinguishing gonorrheal from rheumatic arthritis. When gonococcemia occurs, there may be chills and papulovesicular skin lesions.[49] Bacteriologic study of urethral and cervical smears and of the blood is usually diagnostic.

15. *Chronic meningococcemia* (without meningitis) is characterized by arthralgias without inflammation, continued fever and by characteristic slightly tender, papulo-urticarial cutaneous lesions.[137] Several cases which I observed were confused with rheumatic fever because of the presence of arthralgias and a systolic murmur, and in one case, a prolonged P-R interval (0.22 second). The meningococcus may be isolated from cutaneous lesions or from the blood stream, but cultures should be observed for at least two weeks before they are discarded.

16. *Undulant fever,* like the two preceding, may be characterized by arthralgias and continued fever. Positive blood culture or agglutination reaction, and the history of contact with infected animals or milk, are diagnostic features.

17. *Rat-bite Fever (Haverhill fever).* The rat-bite fever due to the Streptobacillus moniliformis is characterized by fever, polyarthritis and a morbilliform or petechial rash (Haverhill fever). The diagnosis is made by culture of the causative organism from the blood stream.

18. *Ileitis and ulcerative colitis* may simulate rheumatic fever since they are not infrequently characterized by arthralgias or arthritis, fever and erythema nodosum, while the diarrhea is minimal and overlooked.[136] A careful history

and sigmoidoscopic and roentgenologic examination of the intestinal tract disclose the true diagnosis.

19. *Acute appendicitis* is occasionally diagnosed when abdominal symptoms are prominent in cases of rheumatic fever. The difficulty of differentiation has been exaggerated. A careful history usually fails to disclose the characteristic sequence and localization of pain. Vomiting is usually absent. More important, a careful examination usually reveals other features of rheumatic fever such as pleuritis, pericarditis or pneumonitis, joint pains or arthritis, cutaneous or subcutaneous lesions. The pain may respond to salicylates. The sedimentation rate is usually rapid in rheumatic pseudoappendicitis and normal in acute suppurative appendicitis.[82] Rarely, however, a fruitless surgical exploration cannot be avoided. Sometimes also acute appendicitis may complicate rheumatic fever.

20. *Nonrheumatic Forms of Cardiac Disease.* The differential diagnosis is discussed in the chapters on valvular heart disease, pericarditis and endocarditis.

Among other conditions which occasionally simulate rheumatic fever are coccidioidomycosis and rarely actinomycosis.[35]

PROGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

The prognosis of rheumatic fever will be considered under four headings: (1) In the acute attack it is important to know the likelihood of recovery from the acute illness and the duration of the attack. (2) When the acute attack is over, it is necessary to point out the probabilities of recurrent rheumatic attacks and further cardiac damage. When chronic rheumatic heart disease is established, it is desirable to consider: (3) the course of chronic rheumatic heart disease in children, and (4) the course of chronic rheumatic heart disease in adults.

The Acute Attack of Rheumatic Fever

Recovery is the rule in the first acute attack of rheumatic fever. In a series of 20,000 reported cases, Atwater[6] found a mortality of 1.7 per cent in the acute attack. In adults the mortality rate is less than 1 per cent.[168] Death in acute rheumatic fever results from cardiac failure, pericarditis, pneumonia, pulmonary embolization, bacterial endocarditis and toxemia. In more than 75 per cent of the cases active rheumatic infection is the basic cause of these fatal complications.[16] Hyperpyrexia has become a rare cause of death since the use of salicylates.

Higher mortality rates occur in patients with *recurrent* acute attacks, usually associated with carditis and cardiac failure, than in those with their first attack. The distinction between mortality in the initial acute attack and subsequent attacks is seen in the statistics of Hässler and Möller.[63] Of 110 patients suffering their first attack of rheumatic fever, 2.7 per cent died in the acute episode, whereas of the 35 in a recurrent acute attack, 32 per cent died. The latter group is small and the mortality rate unusually high, but undoubtedly the seriousness of the disease and the fatality rate increase with new attacks.

The *duration* of the initial or subsequent acute attacks is variable. Mild cases may hardly reach the clinical horizon or may appear as a simple, febrile, respiratory infection with or without arthralgias, disappearing in a week or two. The more fully developed attack lasts three to eight weeks. This, however, merely represents the average period of obvious clinical manifestations. A

subclinical period of infection indicated by subfebrile temperature, leukocytosis, increased rate of sedimentation of red blood cells, etc., or recurrent exacerbations after brief quiescence may prolong the attack to three to six months or more. In a series of 54 cases studied by Bland,[14] the average duration of active infection was eight months. Persistent rheumatic activity or cardiac failure for longer than six months denotes a serious prognosis.

Aside from those children who die in the acute attack, an additional 10 to 20 per cent never really recover but are left with badly functioning hearts or run a subacute course with persistent rheumatic infection or frequent recurrences of activity at short intervals. Such children remain invalids who spend the greater part of time in bed, require repeated or constant hospitalization and die within two to six years, usually before reaching adult life.

Finally, about 80 per cent of patients with rheumatic fever reach adult life. Many of these have experienced mild attacks or the attack of rheumatic fever is overlooked and surmised later when rheumatic cardiovalvular disease is accidentally discovered. About 65 per cent of children who have had rheumatic fever not only attain adult life but can lead relatively normal lives,[73] either because they have no apparent cardiac disease or because the cardiac lesions are well compensated. The remaining 15 per cent who reach adult life have limited cardiac reserve or definite congestive heart failure and form the bulk of cardiac patients seen in clinics and hospitals. The exaggerated pessimism of statistical data on the prognosis of adult rheumatic heart disease is largely due to excessive weighting by these unfavorable cases.

The Probability and Significance of Recurrent Rheumatic Infections and Cardiac Damage

Following recovery from the acute attack, the prognosis is dependent on (a) the likelihood of recurrences of rheumatic fever and (b) the cardiac damage caused by the first or subsequent attacks. Both of these are closely related to the age at which the initial attack occurs. When the initial attack appears before the age of ten, a recurrence is to be anticipated in 75 to 90 per cent of cases.[89, 121, 17, 166] Thereafter the probability and number of recurrences diminish,[89, 167] and they become infrequent after the age of twenty.

While 20 to 40 per cent of rheumatic patients develop a recurrence within a year after the initial attack, and about 70 per cent within five years, a significant number experience a recrudescence even after apparent good health for five years or longer.[167, 90, 17, 166] According to Cohn and Lingg,[32] and this has also been my experience, recurrence is the rule before puberty and becomes strikingly less frequent thereafter. Wilson and Lubschez,[166] as well as Ehlertsen,[43] stressed not only the age of onset as a determinant of subsequent rheumatic recurrence, but also the interval of freedom following an acute attack. Thus in children below the age of fourteen there was an incidence of about 40 per cent of recurrence within one year after an attack of rheumatic fever as contrasted with a risk of recurrence of 11 per cent following one year of freedom. Practically one may assume that recurrence is improbable when the first attack occurs after the age of twenty, or if five or more years have elapsed since the last attack and the patient is past the age of sixteen. However, under the stress of military training, crowding and constant reexposure to new recruits, rheumatic recurrence was not uncommon in young adults who had long been free of rheumatic activity.

The incidence of significant *cardiac damage* in the initial attack of rheumatic fever varies between 30 per cent and 80 per cent of cases, according to the age at the initial infection.[111] Cardiac involvement is most likely when the first rheumatic attack occurs between the ages of five and ten. The probability of cardiac involvement diminishes as the age of initial infection increases, and becomes particularly infrequent when the first attack of rheumatic fever occurs in adult life.[39, 77] On the other hand, Brown[23] emphasizes neither the age of onset nor the number of infections, but the resistance or immunity of the patient to cardiac damage. According to Brown, patients who show no permanent cardiac damage in the first attack are likely to escape such damage in subsequent rheumatic recurrences.

The occurrence of *subcutaneous nodules* has usually been associated with concomitant carditis and therefore with an ominous prognosis.[22] *Rheumatic pericarditis* is serious both because of relatively high acute mortality and the probability of permanent cardiac damage. In 135 cases of acute rheumatic pericarditis studied by Massie and Levine,[96] there was an acute mortality of 16 per cent in an average period of 5 weeks, a further mortality of 30 per cent among 82 of these patients who were followed for a subsequent average period of 6.7 years. On the encouraging side was the remarkable finding that 36 per cent of those followed had no clinical evidence of organic heart disease. A more serious outlook is indicated by the observations of Ash,[2] who found that 75 per cent of 553 children with rheumatic pericarditis were dead after a follow-up period of 9.6 years. Other evidences of *carditis,* such as cardiac enlargement and diastolic gallop rhythm, but especially congestive heart failure, are also associated with a very high acute mortality, or with a high incidence of severe and permanent organic heart disease.

Chorea in itself does not denote an unfavorable prognosis with respect to the probability of cardiac involvement. However, other rheumatic manifestations eventually develop in the majority of cases of chorea and the incidence of cardiac disease is determined by these other rheumatic features. Jones and Bland,[72] in an analysis of 482 cases of chorea, observed an incidence of only 3 per cent of heart disease among 134 patients with chorea alone, while among 184 patients with chorea and other evidences of rheumatic fever, heart disease was discovered in 80 per cent.

Considering the entire course of the disease, it is probable that 65 to 75 per cent of children who suffer from rheumatic fever develop clinical heart disease with their first or subsequent attacks.[34, 47, 1, 73] If electrocardiographic changes or slight cardiac enlargement associated with systolic murmurs are accepted as evidence of organic heart disease, then at least 90 per cent of patients with rheumatic fever may be considered as developing rheumatic heart disease.[165] While microscopic examination might reveal some cardiac damage in practically all patients with rheumatic fever, it is important from the point of view of prognosis to distinguish the 25 to 35 per cent of children who fail to show clean-cut clinical evidence of organic heart disease. However, in about one quarter of such subjects signs of permanent valvular deformity not present at the time of the original illness appeared in the next ten years.[17] So long as such evidence does not appear, one must assume that these patients have minimal cardiac damage and therefore are entitled to a good prognosis.[4, 3] The prognosis in the remaining patients, with obvious clinical heart disease, must be evaluated separately according as they are children or adults.

The Course of Chronic Rheumatic Heart Disease in Children

The outlook for the child with rheumatic heart disease is generally regarded as unfavorable. Wilson and her associates[167] in a ten year follow-up of 395 children with rheumatic fever and heart disease observed that 12 per cent had died within that period, usually between the ages of eleven and fourteen. In a subsequent study of 717 such cases Wilson[165] noted that 18 per cent had died within an average period of eight years after the onset of rheumatic fever. Stroud, Bromer and associates,[141] in a similar study of 458 rheumatic children, found that more than 20 per cent were dead within ten years after the initial rheumatic attack, and another 20 per cent were totally disabled; in a more recent ten year study from the same institution the mortality rate had fallen to 15 per cent.[143] Martin[93] studied some 1400 children with inactive rheumatic heart disease over a twenty year period. About 30 per cent were dead at the end of that period, 10 per cent having died after two years and 26 per cent after twelve years. Other studies disclosed mortality rates varying from 24 per cent[70] to 12 per cent[126] after ten years of observation. All these studies disclose that the great majority of fatalities occur below the age of twenty.

The chief danger lies in the probability of acute recurrences with a concomitant increase in cardiac damage. Each new attack brings with it its percentage of acute mortality, of cardiac failure or of progressive cardiac damage. Thus the difficulty of prognosis in childhood lies not only in evaluating the effect of existing cardiac damage on life expectancy, but in predicting what further injury will be wrought by subsequent attacks.

If the child shows evidence of *right heart failure,* the prognosis is very poor; it is doubtful whether he will survive puberty.

The existence of *auricular fibrillation* also warrants a serious prognosis, in that it denotes extensive myocardial damage. Auricular fibrillation in rheumatic cardiac children occurs in fatal cases, and usually develops a few months before the end.[130, 33, 142] However, this must be distinguished from the adult cases of rheumatic heart disease in which auricular fibrillation may persist for as long as fifteen years.[79]

According to Cohn and Lingg[32] the *severity of the rheumatic infection* determines the subsequent course. When the infection was classified as *very* severe, only 34 per cent, when severe, only 56 per cent, survived childhood, and only 7 and 12 per cent respectively survived adolescence. With milder attacks 70 per cent survived childhood and 35 to 60 per cent survived adolescence.

Signs of *persistent active rheumatic infection* in a child with rheumatic heart disease always call for a guarded prognosis. This applies particularly to the cases in which there is active carditis. The outlook is especially serious if evidences of activity persist for more than six months. On the other hand, if there is no cardiac failure, if the cardiac rhythm is normal, and if all signs of active infection subside, the prognosis as to the organic cardiac lesion is temporarily improved. But the child has only overcome the first hurdle and the ultimate prognosis depends on his luck in avoiding subsequent attacks and subsequent cardiac damage. Practically, it may be considered that the early prognosis is greatly improved when puberty is passed, when there are no longer signs of active rheumatic infection, and when five years or more have elapsed since the preceding attack. When this period is continued into maturity and the

cardiac lesions remain well compensated, the prognosis becomes increasingly favorable.

The Course of Chronic Rheumatic Heart Disease in Adults

We have seen that the average prognosis of rheumatic heart disease in children is poor. If the duration of life after the initial infection or the age at death is so calculated as to include patients dying in childhood or early youth, the average prognosis appears much worse than if these figures are determined among purely adult groups. It appears to me to be important to make such a segregation because the problem confronting the pediatrician or cardiologist who must give a prognosis regarding a *child* with rheumatic heart disease is quite different from that confronting the physician who attends an *adult* rheumatic cardiac patient. For the latter has already overcome the serious dangers which are associated with recurrent or persistent rheumatic infections of childhood, and which are the very elements that make prognosis unfavorable in earlier life. The very fact that these adult individuals have come to maturity despite recurrent rheumatic infections indicates that the functional and anatomic damage in these individuals was least serious.

I should like to distinguish between the statistical averages in prognosis and the outlook for the individual patient. In the following sections these averages are presented, but an attempt is also made to state the factors which influence the prognosis in the individual case. For the physician, the art of prognosis lies in his ability to evaluate the chances of the individual patient for a more or less favorable course rather than in his knowledge of the hypothetical average.

The Duration of Life after the Initial Infection and the Age at Death. The duration of the disease can only be determined in patients with a definite history of rheumatic fever. In general this duration, as determined, is minimal because the first *manifest* attack of rheumatic fever often follows previous unnoticed attacks and perhaps appears after cardiac damage is already present. In statistics based on clinical material, the average duration appeared to be fifteen years in the group which succumbed during the period of study.[163, 38] On the basis of cases verified by postmortem examination, I have found the average duration to be twenty-three years.[50] Coombs[34] estimated the duration of the disease to average thirty years. It is important to emphasize that there are pronounced variations in all of the series considered. It is quite probable that the average duration of life after the initial infection is considerably longer in the experience of the general practitioner than that of the cardiologist. But even in the series studied by de Graff and Lingg,[38] 46 of their 644 patients lived for more than thirty years, and some for more than forty years. In a special group of patients in whom rheumatic heart disease was discovered at postmortem examination, the duration of life after the initial infection averaged thirty-eight years, and 25 per cent of the patients lived for more than fifty years after the first rheumatic attack.[50] In cases of rheumatic calcific aortic stenosis, the duration of life after the initial infection often is essentially normal (p. 614).[27]

The average *age at death* is variously stated as lying between thirty and forty-five years.[163, 38, 50] These figures are much higher if only well compensated rheumatic cardiacs who have reached early adult life are included. But even in the more comprehensive statistical studies, a variable percentage (10 to 35 per

cent) of patients survive the age of fifty, and occasional individuals with rheumatic heart disease live beyond seventy.

It is not intended to minimize the serious prognosis of rheumatic heart disease. But in view of the general pessimism with regard to this ailment, it is important to emphasize that not every rheumatic cardiac is doomed by the unfavorable averages of the group. Every series of statistics on rheumatic heart disease includes a number of patients who have lived a normal or an unusually long span of life. I[50] had the opportunity of observing many such cases, in a study of individuals who died in a city home. These patients were mostly of advanced age. While there were physical signs of valvular heart disease, there were no cardiac symptoms except in a group of patients whose death was due to cardiac failure. The presence of rheumatic heart disease was verified by postmortem examination. The average age of death was sixty-five years. There were 100 such autopsied cases in five years and these formed 10 per cent of the total number of autopsied cases during that period. Thus, long-lived cases of rheumatic heart disease are by no means rarities, but they are not generally observed in hospitals or clinics which patients attend because of persistent cardiac symptoms.

Factors Influencing the Course of Rheumatic Heart Disease in Adults. The following factors may be considered in distinguishing the patients with favorable or unfavorable outlook:

The *economic and social status* of the patient appears to be a most significant factor, once the stage of active infection is over. The most unfavorable course is observed in the poorest patients, who are encountered in city hospitals or clinics or other charitable institutions. Unfortunately most statistical studies are based on these patients, a fact which accounts in part for the very unfavorable average duration of life ascribed to rheumatic cardiacs. On the other hand, if the rheumatic patient, because of his economic status, can avoid the more serious physical and mental strains of life, if he can avoid fatigue, or rest when he is fatigued, if he can properly take care of every illness, however minor, avoid the inclement effect of weather extremes by seasonal change of his environment, and especially if he can avoid the respiratory infections which come with overcrowding, his outlook may be considered quite favorable, provided that the cardiac damage already done is not severe. A high economic and social status may help to provide other favorable factors such as good nutrition, a desirable occupation and an intelligent mental outlook, all of which may play a role in prolonging life.

The *functional state of the heart* is of primary importance in prognosis, but unfortunately this cannot always be evaluated with a high degree of accuracy. The presence or absence of cardiac symptoms in the course of normal activity is as good a practical indicator as any. The patient whose cardiac lesion is discovered on routine examination or on examination for minor noncardiac ailments has a much more favorable outlook than the patient who constantly requires medical attention because of dyspnea, limited cardiac reserve on exertion, or some other symptom directly due to his rheumatic heart disease.

The *degree of cardiac enlargement* has been utilized as an indicator of prognosis in rheumatic heart disease. From a ten year follow-up study of 1000 ex-service men with valvular heart disease, Grant[53] concluded that in general the duration of life diminished in proportion to the degree of cardiac enlargement.

However, it is important to consider the type of valvular disturbance. Thus, in aortic lesions, cardiac enlargement is usually much more pronounced than in mitral lesions although the prognosis is no less favorable. Grant's study included cases of syphilitic aortic insufficiency which are associated with very large hearts and a less favorable prognosis than in rheumatic cases. Inclusion of these cases tended to exaggerate the prognostic importance of cardiac enlargement. However, in general, one may say that for any given valvular deformity the worst prognosis should be applied to patients with more pronounced degrees of cardiac enlargement.

The *age at the initial infection* is not a prognostic aid in adults as it is in children. After maturity the subsequent duration of life diminishes, as the age at the initial infection increases.[163, 50] This is probably due to the normal diminution of further life expectancy with increasing age. The average age at death is generally greater in individuals acquiring the disease later in life. This merely indicates that with a great span of life already covered, even a brief further duration may give a relatively normal total life span.

The *number of rheumatic recurrences* is also insignificant for prognosis in the adult rheumatic cardiac.[50] The fact that the patient has passed maturity indicates that the myocardial damage was not of the most serious type, which rapidly results in death. If, furthermore, the functional state of the myocardium is good, compensation has been effected regardless of the number of attacks. These are now only a matter of past history. In any event, statistical studies of adult rheumatic cardiacs fail to show any constant relationship between the number of rheumatic attacks and the age at death.

The *nature of the valvular lesion* also bears no constant relationship to the duration of life.[50, 37, 38] But rheumatic calcific aortic stenosis (p. 614) is often found in men in the sixth or seventh decades of life.[27] Tricuspid stenosis (p. 624) is associated with an earlier average age at death than other valvular lesions.

The occurrence of *left and right heart failure* is a serious prognostic omen. The statistics of Friedberg and Tartakower[50] and of de Graff and Lingg[38] indicated that the duration of life after the onset of failure averaged two and one-half to three years, and that one third to one half of rheumatic patients suffering right heart failure died within one year. This outlook has definitely improved since the generous use of mercurial diuretics. The prognosis of patients with left-sided heart failure of mild degree is not so serious as that of rheumatic cardiacs with right-sided heart failure. Many patients with mild cardiac dyspnea live for ten or more years.

Auricular fibrillation develops in one quarter to one half of cases of rheumatic heart disease, particularly in the presence of mitral stenosis.[99] It is of ominous portent, generally developing late in the course of the disease. The duration of life after its onset averages less than two years. Nevertheless, the average age at death of rheumatic cardiacs with auricular fibrillation is high because fibrillation usually develops in those who have already had a long period of survival. Although the prognosis is generally poor in adult rheumatic cardiacs with this arrhythmia, not infrequently they live without serious discomfort for ten or more years,[79] if the ventricular rate is slow.

The *sex* of patients with rheumatic heart disease is of no significance in prognosis. While women are subjected to the strain of pregnancy and childbirth,

men experience greater physical and psychic stress in connection with their occupations and are more exposed to infection.

Causes of Death in Rheumatic Heart Disease

In children with rheumatic heart disease, death in the great majority of cases is due to active rheumatic infection[16, 93] with resulting pancarditis, heart failure, pneumonitis, pulmonary infarction and toxemia.

Among adults, congestive heart failure is the commonest cause of death, usually without but not infrequently with concomitant active rheumatic disease.[83, 74] Bacterial endocarditis, embolization, pulmonary infarction and bronchopneumonia and arteriosclerotic coronary occlusion are among the other causes of death.

Sudden death is much less common than in cases of arteriosclerotic coronary disease or cardiovascular syphilis. Its most frequent occurrence is in patients with aortic stenosis.[94] Its advent in aortic insufficiency has been exaggerated due to inadequate segregation of cases due to syphilis. In mitral stenosis, sudden death may result from embolization, ventricular fibrillation or ball valve thrombus.

THE TREATMENT OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Before presenting a detailed discussion of treatment, it is important to emphasize that there is no specific therapy of proven value and that the prevention of rheumatic heart disease is probably more of an economic problem than a medical one. Let us not be too dogmatic in the execution of the recommended therapeutic measures. The preliminary report of the beneficial effect of compound E (17-hydroxy-11-dehydrocorticosterone), a hormone of the adrenal cortex, and of pituitary adrenocorticotropic hormone on rheumatoid arthritis and rheumatic fever suggests a new approach to the therapy of the disease under discussion.[63a]

The Acute Attack of Rheumatic Fever

1. Bed Rest. Absolute confinement to bed is the most vital element of the treatment of the active stage of the disease. This includes pleasant surroundings and facilities for diversion if possible. There is considerable disagreement as to the proper duration of bed rest. It may be accepted as a general principle that this period should be at least as long as there is rheumatic activity. In order to be certain that the absence of fever and other rheumatic symptoms is not due to salicylates or other antipyretics, these drugs should be discontinued at least temporarily. If the patient remains afebrile for the next four to seven days without these drugs, and if there is no tachycardia (sleeping pulse), laboratory tests should be performed to determine rheumatic activity. The disease may then be considered inactive if the leukocyte count and erythrocyte sedimentation rate are normal, and the patient begins to gain weight. When this stage is reached, some physicians wait another two or three weeks before permitting the patient to leave his bed, in order to gain additional assurance that the disease is really inactive. Occasionally there is a persistent tachycardia without other evidence of activity. In such cases I have not infrequently observed a good response to the gradual resumption of activity.

Longer periods of bed rest are necessary for children than for adults because of the greater probability of cardiac damage and the greater danger of rheumatic recurrence in the former, and because of certain dangers of prolonged bed rest in the latter (p. 162). In the mature adult, the above period of bed rest may be somewhat diminished when there is no evidence of carditis and when an early return to work is of vital importance. Not infrequently, two or three months or even longer may elapse after the disappearance of fever and subjective symptoms before all signs of activity are gone. There may only be an increased sedimentation rate or tachycardia at rest. For practical reasons one is often compelled to compromise and allow both children and adults out of bed despite the theoretic presence of rheumatic activity if the temperature has been normal for four to six weeks and there are no rheumatic symptoms. Usually they are apparently none the worse for this concession, but occasionally there is a recurrence of symptoms and they must return to bed.

2. Diet and Regimen. The principle of the *diet* is to maintain nutrition in a febrile disease which is apt to be of long duration.[109] When there is moderate or high fever, the diet must be limited to fluids only and these must be rich in calories. Vitamins and minerals may then have to be supplied in concentrated form. Since most of the patients are growing children, an adequate protein intake is essential. As with other febrile infections, fluids should be forced (at least 2500 to 3000 cc. daily). It is especially important in rheumatic fever when there is a large fluid loss through excessive perspiration. In the presence of congestive heart failure, an extremely low salt diet should be given (p. 166).

Nursing care is of the greatest importance in the management of the rheumatic patient. Appetite is capricious at best, and is further impaired by fever, drugs and inactivity. The appetite may be partially improved if high temperatures are controlled by sponging and by salicylates. The preparation and serving of food should be made especially attractive. The contribution of napkins, tray, dishes and silverware to the inviting appearance of the food are elements not to be regarded with cavil. Small quantities of food should be served frequently (e. g., every two or three hours), but not so frequently as to disturb the patient unduly. For the same reason, procedures such as meals, medication, bathing, changing underwear, should be concentrated so that adequate undisturbed intervals allow the patient to obtain rest and sleep.

A comfortable bed and a fair-sized room with adequate ventilation and sunshine are perhaps trite but nevertheless important essentials. Drafts are especially apt to be dangerous when there is frequent and excessive perspiration. For this reason also the patient should be clothed in light wool sleeping garments, which can be removed easily and without disturbance. Since frequent changes are necessary to keep him dry, a zipper arrangement down the front and sleeves is useful; or else the pyjamas can be worn back side front so that they are open behind and can be easily removed without making the patient sit up. With each change the perspiration should be wiped away with warm water, preferably mixed with dilute alcohol. This will generally prevent the development of a sour odor from accumulated perspiration.

Cathartics or enemata may be necessary while the patient is in bed. Mild cathartics, such as aromatic extract of cascara or milk of magnesia, are usually satisfactory, but in general the patient should be permitted to choose the cathartic and dosage which ordinarily produce the desired effect.

3. Drug Therapy. *Salicylates.* Stricker,[139] who first recognized the therapeutic value of salicylates in rheumatic fever, considered them to be a specific cure for the disease. While their specificity is no longer accepted, prolonged usage has established their antipyretic and analgesic effects, their striking relief of joint pain and swelling and their beneficial influence on the general well being of the rheumatic patient. These rapid and impressive therapeutic effects of salicylates are so characteristic that they have been considered diagnostically important. However, a similar response may occur in other febrile states and occasionally such improvement is lacking in definite cases of rheumatic fever. Hanzlik[59] noted complete relief of all symptoms in 81.8 per cent of 400 rheumatic patients receiving sodium salicylate, and complete failure in 1.6 per cent. Persistence of fever and discomfort despite full doses of salicylates usually indicates severe and spreading infection or visceral complications, but occasionally denotes only a constitutional difference in a patient who fails to show the usual therapeutic response.

Since Pribram's[113] observations, it has been taught that salicylates do not reduce the duration of the active infection. More recent studies have also indicated that the duration of rheumatic activity and the hospital stay of salicylate-treated and untreated patients did not differ significantly.[102, 98] The question is far from settled because of the varied duration of individual cases and because the statistics available are not uniform in their criteria for subsidence of infection.

It has long been taught that salicylates do not prevent cardiac complications and that pericarditis, heart failure, pleuropulmonary symptoms and subcutaneous nodules have frequently developed in rheumatic children under full salicylate dosage.[102, 44, 105, 60] On the other hand the evidence that salicylates modify the action of metabolic processes and enzyme systems,[88] and especially that they inhibit the spreading effect of hyaluronidase, has suggested a more specific effect on rheumatic fever.[57] More recently Coburn[29] has claimed that intensive therapy sufficient to maintain a continuous salicylate plasma level of at least 35 mg. per 100 cc., instituted early in the acute phase of rheumatic fever, not only rapidly suppressed the infection but also reduced the incidence of polycyclic recurrences and residual chronic activity, and prevented cardiac residua. These claims have been supported by Peters but not by others who have used Coburn's therapeutic regime.[110, 155]

It is probable that salicylates control the exudative phase of cardiac inflammation, but not the proliferative. I have repeatedly seen the rapid subsidence of a large pericardial effusion in rheumatic patients who appeared critically ill when salicylates were administered in massive doses throughout the night and day.[20] Indirectly also, salicylates may benefit the course of rheumatic carditis by controlling fever, tachycardia, pain, discomfort and insomnia.

ADMINISTRATION AND DOSAGE OF SALICYLATES. Salicylates are administered *orally* in the form of *sodium salicylate* or *acetylsalicylic acid,* in sufficient dosage to obtain a satisfactory control of fever and pain, or to the point of toxic manifestations. Sodium bicarbonate is given with salicylates (infra). The full therapeutic dose of sodium salicylate in *adults* is 10 to 12 gm. daily, but this produces toxic symptoms in most patients.[91] Usually 6 gm. daily suffices, 1 gm. (15 grains) being given every four hours day and night. Thereafter the dosage is increased if a satisfactory response is not obtained. Mild nausea and tinnitus

are not contraindications to a given dosage if this is essential for the control of fever and other symptoms. Salicylate therapy is continued until fever and other signs of rheumatic activity have been controlled for one to two weeks. Salicylates are then discontinued but may have to be resumed promptly if there is a reappearance of the clinical or laboratory manifestations of rheumatic fever.

The corresponding dosage of sodium salicylate in *children* is 4 to 8 gm. daily. In practice I commence with 0.65 gm. (10 grains) every four hours throughout a twenty-four hour period and increase either the dose or frequency until the desired therapeutic effect is obtained. If toxic symptoms appear, the dose is reduced, preferably after discontinuing the drug for twelve to twenty-four hours.

Acetylsalicylic acid is frequently used instead of the sodium salt.[64a] About three quarters as much as the recommended dose of sodium salicylate will produce identical effects. It is best administered in tablet form. Enteric coated tablets, recommended to avoid gastric irritation, may disintegrate slowly and accumulate in the colon instead of being absorbed from the upper gastrointestinal tract. A toxic effect may be produced by sudden absorption of the accumulated tablets.[67] *Methyl salicylate* is used locally by the laity in the form of oil of wintergreen and various patented preparations; but its effects are due to counter-irritation alone, as there is inadequate absorption to produce significant systemic action.

Sodium bicarbonate is administered with salicylates, either as half the dose of sodium salicylate or in equal doses with acetylsalicylic acid. The alkali serves to diminish gastric irritation caused by the salicylates. According to Peters[110] the toxic effects of very large oral doses of salicylates can be prevented by the simultaneous administration of twice the dosage of sodium bicarbonate in solution.

In patients with rheumatic carditis and congestive heart failure the possible danger of administering significant quantities of sodium must be taken into account. Furthermore, large doses of sodium bicarbonate diminish the blood level attained with a given dose of salicylates[134] by (a) increasing the renal excretion of salicylates,[26] (b) diminishing gastric absorption of salicylates since sodium bicarbonate elevates the pH of the stomach, (c) increasing the amount of extracellular fluid and therefore diminishing salicylate concentration.

Occasionally a satisfactory therapeutic response is not obtained even with large doses of salicylates and it is found that the plasma level of salicylates is relatively lower than expected with the given dose. In such cases Dry and associates[41] have noted that para-aminobenzoic acid, administered orally, elevated the salicylate blood level, perhaps by competitive renal excretion, and thereby produced the desired therapeutic effect.

The *toxic manifestations* of salicylates[46, 123, 52] include tinnitus, deafness, vertigo, headache, nausea and vomiting, and occasionally diarrhea. Although there is some direct gastric irritation, the toxic gastrointestinal symptoms are due to salicylate action on cerebral centers.[26] More serious evidences of salicylate intoxication are dermatoses, excessive vomiting, Kussmaul respiration due to acidosis, tetany due to hyperventilation, delirium, mania, hallucinations, coma and death.[11, 122, 62]

Severe dyspnea from excessive doses of salicylates has been attributed either to fixed acid acidosis or medullary respiratory stimulation.[69, 46, 64a] According to Manchester[91] the depletion of alkaline reserve following large doses of

salicylates is preventable by the simultaneous administration of adequate quantities of alkali.

Hypoprothrombinemia occurs after a few days of intensive salicylate therapy.[101, 24, 107] This is usually insufficient to produce hemorrhagic phenomena and the prothrombin time gradually returns to normal despite continued salicylate therapy. However, hemorrhagic complications and death have been attributed to salicylate therapy.[5] The administration of vitamin K restores a prolonged prothrombin time to normal.[132]

Intravenous administration suggested by Mendel[100] was long employed by French physicians.[87, 12] Recently Coburn[28] has revived interest in this method of administration in connection with his advocacy of large salicylate dosage and the early and continuous maintenance of high blood levels of salicylates. Ten grams of sodium salicylate are dissolved in 1 liter of normal saline and introduced intravenously in a period of four to six hours. If rheumatic symptoms persist or the temperature does not return to normal, 20 gm. of sodium salicylate is administered in 2000 cc. of 0.9 per cent sodium chloride solution, in a period of eight hours. If this is effective, the dose is diminished to 10 gm. daily, if possible. To counteract acidosis Ringer-lactate solution may be used instead of normal saline. The sodium salicylate infusions are repeated daily for one or two weeks. Thereafter, 10 gm. of salicylates may be administered daily by mouth in divided doses until all signs of rheumatic activity have been controlled for two weeks. There is no consistent evidence that the intravenous use of salicylates in large doses yields superior results to those obtained by corresponding oral doses.[160, 155] On the other hand there is a much higher rate of severe toxic disturbances.[160, 92]

Rectal administration has been recommended when there is gastric intolerance or difficulty in oral administration in young children.[64] When vomiting is due to toxic doses of salicylates, the change from oral to rectal administration is purposeless since the symptom is of central origin. According to Huntington and associates,[67] the rectal absorption of salicylates is poor and no appreciable amounts reach the blood stream, but this appears to be contrary to previous clinical experience.

Following a cleansing enema, 5 to 10 gm. of sodium salicylate dissolved in 4 to 6 ounces (120 to 180 cc.) of thin starch paste containing 1 cc. of tincture of opium is slowly instilled into the rectum. This is repeated in twelve hours if there are no symptoms of salicylism. If preferred, 3 to 4 gm. of sodium salicylate in 120 cc. of starch solution can be instilled as a retention enema four times daily.

Cinchophen and Its Derivatives. The action of cinchophen and its derivatives is similar to that of salicylates.[106, 21] They may be tried when a patient appears to be intolerant of therapeutic doses of salicylates. Attention is directed to reports of toxic hepatitis following the administration of cinchophen.[115] *Cinchophen* is administered in the same doses as sodium salicylate (6 to 12 gm. daily in divided doses for adults; 4 to 8 gm. daily for children). Somewhat larger doses of *neocinchophen* (tolysin) are necessary (1.3 gm. of neocinchophen for 1 gm. of cinchophen), but there is less gastric irritation.

Aminopyrine. Aminopyrine is quite effective in rapidly reducing fever and relieving the joint symptoms of rheumatic fever.[127] It possesses the advantages of producing neither the local gastric irritation nor the toxic effects of salicylates and does not require the simultaneous administration of sodium bicarbonate.

It may be especially preferred in cases of rheumatic fever with heart failure in which the administration of sodium salts is undesirable. The one great disadvantage is the occasional production of agranulocytosis in sensitive persons.

The dose of aminopyrine is about one third that of the salicylates. In *adults* 2 to 3 gm. daily may be given in divided doses at four-hour intervals; in children 1.5 to 2 gm. daily.[128] While 3 gm. daily is considered the maximum daily dose, it is probable that 4 or 5 gm. daily would correspond more closely in therapeutic effect to the massive doses of salicylates (10 to 12 gm. or more) recently recommended. Because of the danger of agranulocytosis, frequent blood examinations are essential.

Antipyrine, acetphenetidine, benzoic acid and quinine have also been employed for their antipyretic action, but none of these are as effective as the salicylates, cinchophens or aminopyrine. Recently Gubner and Szucs[56] reported the favorable action of a calcium double salt of benzoic acid and succinic acid benzyl ester, but this was not confirmed by Wégria and associates.[161]

Digitalis is indicated and effective in the treatment of acute rheumatic fever when there is associated heart failure with or without auricular fibrillation. Its administration is discussed on pp. 183-188. Sutton and Wyckoff[147] have reported beneficial effects in children with right-sided congestive heart failure, active rheumatic infection and normal sinus rhythm; similar favorable results with digitalis were obtained by Walsh and Sprague.[154] Often the therapeutic effects are not striking or are absent, and the rapid heart rate is unmodified because of the activity of a severe rheumatic infection. Furthermore, for the same reason there is a tendency to increase the dose of digitalis to dangerous levels; there are frequent instances of digitalis toxicity, including the production of premature beats, heart block, auricular fibrillation, ventricular tachycardia or even fibrillation.[19, 129]

Mercurial diuretics should be administered when heart failure is present, as discussed in Chapter 9. The usual dose in children is 0.5 to 1 cc. The danger of digitalis intoxication during diuresis should be remembered (p. 198). Walsh and Sprague[154] have reported good results from the use of the xanthine diuretics, especially theocalcin (theobromine calcium salicylate) and thesodate (theobromine sodium acetate), either being given in doses of 1 gm. three or four times daily. I have rarely observed the need for the xanthine diuretics when the mercurials can be given; nor have the results been comparable to those obtained with the latter diuretics.

Oxygen therapy is indicated in the presence of severe respiratory distress or cyanosis due to pulmonary infarction or pneumonitis or to heart failure with pulmonary congestion or pulmonary edema.

Morphine is rarely indicated and should be administered with caution. It is occasionally desirable for the intense dyspnea of acute pulmonary edema or for very severe pain at the onset of rheumatic fever before salicylates become effective. Codeine may be needed to control precordial pain or cough. Sedatives or soporifics are frequently beneficial during the most acute phases of the disease.

Antibiotics: Sulfonamides and Penicillin. Neither the sulfonamides[149] nor penicillin[157, 48, 117] is beneficial in the treatment of rheumatic fever and may be definitely harmful. Their prophylactic use to prevent hemolytic streptococcal infections and rheumatic recurrences is discussed below. Penicillin may be

given during active rheumatic fever in the presence of bacterial infections which yield to that antibiotic.

4. Pleural and pericardial paracenteses are rarely necessary even in the presence of large effusions. Administration of adequate continuous dosage of salicylates almost always prevents or relieves pericardial effusions.[20] If not, a pericardial tap can be best performed posteriorly, slightly to the left of the angle of the left scapula in the eighth interspace.[145] If this is unsuccessful and a large pericardial effusion is definitely present, the needle may be inserted anteriorly in the fourth or fifth left interspace about 2 cm. within the left border of dullness.

5. Tonsillectomy. At one time tonsillectomy was generally recommended to prevent rheumatic recurrences. This was based on the belief that the tonsils harbored causative streptococci or that they were the portal of entry of the causative organism of rheumatic fever. Statistical surveys on the effect of tonsillectomy have been inconclusive or contradictory.[75, 167] The indications for tonsillectomy appear to be the same whether or not the individual concerned has ever had rheumatic fever. It is generally considered inadvisable to perform a needed tonsillectomy until several months after an episode of active rheumatic fever. Penicillin should be administered immediately prior to and for several days after the tonsillectomy if the patient has a valvular lesion, in order to avoid a complicating bacterial endocarditis (p. 804).

6. Roentgen Ray Therapy. Roentgen rays have been employed in rheumatic fever because of their usefulness in other infections. Levy and Golden[86] administered small doses of roentgen ray over the front and back of the precordial region in 30 patients with varied types of rheumatic heart disease. Improvement, as indicated by electrocardiograms, was noted in 70 per cent of the cases. In a recent controlled study, Griffith and Halley[55] were unable to confirm these findings.

7. Fever Therapy. Fever therapy with typhoid vaccine and radiant energy has been employed in both active rheumatic carditis and chorea (p. 769).[42, 146] The value or possible risks of these procedures is still sub judice.

8. Blood Transfusions. Blood transfusions have been administered in acute rheumatic fever with the idea of increasing immune bodies as well as improving the anemia.[162] Even small transfusions must be administered with caution because of the danger of inducing or intensifying heart failure. This is less likely to occur if the transfusion is given in the form of packed red blood cells in small quantities of 5 per cent glucose in distilled water. In the presence of heart failure, severe anemia may be detrimental to restoration of cardiac reserve. Small transfusions of packed red blood cells may be beneficial but should be preceded by a mercurial diuretic four to eight hours earlier in order to avoid the precipitation of acute pulmonary edema.

Convalescence and Rehabilitation

Convalescent Homes and Sanatoria. Convalescence does not properly begin until all signs of active infection have disappeared. Discharge from a hospital ward to make room for more acutely ill patients does not necessarily denote that the rheumatic patient is ready for convalescence. Neither does removal to a convalescent home label the patient as "convalescent" if he still shows active rheumatic infection. So long as there is activity, the patient is properly a bed patient. The analogy between rheumatic heart disease and tuberculosis

as regards pathogenesis, pathology and clinical course may be extended also to treatment. The treatment of rheumatic heart disease, like that of tuberculosis, could best be administered in specially segregated wards or hospitals. Patients with active rheumatic heart disease cannot be treated properly if they must compete for beds with those with the ordinary acute illnesses.

In cognizance of these problems, organizations in this country and in England have undertaken to care for convalescent cardiacs in special convalescent homes or hospitals. In such institutions there are not only the advantages of continued and prolonged medical and nursing care for the patient but also opportunities for controlled study of the disease, for research and for the early discovery and treatment of rheumatic reactivations. In addition the patient receives instruction in the rules of hygiene, the psychologic advantages of group play and exercise, schooling and occupational therapy during the intermediate period between active illness and the resumption of a relatively normal life. Unfortunately from the patient's point of view, the results have not always been impressive. One of the most disconcerting features of these convalescent homes has been the occurrence of epidemics of streptococcal infections and rheumatic fever.

Resumption of Physical Activity. Physical activity may be resumed during convalescence, but it should be increased more gradually than after other febrile diseases. As a rule physical activity is not undertaken until there has been a two week period during which, in the absence of salicylates, there is no fever, carditis, arthritis or other clinical or laboratory evidence of rheumatic activity. On the other hand, these strict criteria may necessitate such prolonged bed rest that cardiac anxiety neuroses are induced. To avoid this, Robertson, Schmidt and Feiring[119] permitted moderate early privileges, such as sitting in a chair, going to latrine or shaving, depending on the patient's general clinical condition and comfort rather than on strict laboratory data.

Ordinarily the rate of progress of physical activity is determined in part by the presence and extent of cardiac damage and especially by the clinical response of the patient to increasing activity. Various exercise tests have been employed to gauge progress and as a guide to the degree of activity permissible. With the aid of a step-test, Karpovich and associates[76] devised a program of physical reconditioning for soldiers convalescing from rheumatic fever. Graded exercises were given according to the response to the exercise test. They were able to begin these exercises safely within two weeks after clinical cessation of rheumatic activity and to reduce the conventional delay in beginning reconditioning from an average of seventy-seven to an average of sixteen days without any increase in cardiac damage.

Treatment of the Chronic Inactive Stage of Rheumatic Heart Disease

Essentially this involves the management of patients with rheumatic valvular heart disease (Chapters 26 to 29). When auricular fibrillation, heart failure or bacterial endocarditis develops, treatment follows the principles set down elsewhere under those headings. Aside from these and other complications, the patient with inactive rheumatic cardiovalvular disease may rarely seek medical attention, and then only for some unrelated condition. Treatment during this period consists of instruction in hygienic living, avoidance of streptococcal and other infections, advice as to sociologic and economic problems, and not the least, optimistic encouragement.

Exercise. When the stage of convalescence is passed and circulatory compensation is attained, the problem of exercise is not formidable. Restriction of physical exertion, formerly stressed as a vital point in the treatment of inactive heart disease, does not appear warranted when there is satisfactory compensation. For some time after an acute attack, a moderate degree of dyspnea, tachycardia and palpitation may result purely from prolonged bed rest and lack of physical training, independent of cardiac disease. Prolonged overprotection from physical exercise, even after rheumatic activity has ceased, serves only to protract the abnormal symptoms produced by even slight exertion. Except for the most rigorous sports involving unusual speed and endurance, such as rowing, long distance running, tennis, etc., I do not believe it important or wise to restrict the well compensated inactive rheumatic cardiac patient. A moderate degree of consistent physical activity is of advantage in bringing about the efficiency of circulatory, respiratory and metabolic economies which result from training and which would appear to be of special value to the cardiac patient. So long as there are no evidences of circulatory failure, moderate exercise is of as much value to the rheumatic cardiac as to the normal person. The degree and amount of exercise permitted depends on the individual's symptomatic response, undue fatigue and dyspnea being the stop signals.

Prophylaxis. *General Measures, Vaccines, Air Sanitation.* The objective of prophylaxis is the elimination of recurrent rheumatic activation. The importance of improved housing conditions and avoidance of crowding has been discussed (Chapter 31). Adequate rest and sleep and proper nutrition are essential for maximal resistance against infection. Jackson and associates[68] presented evidence that rheumatic recurrences in children were strikingly diminished by placing them in a favorable environment where proper nutrition was provided.

Hemolytic streptococcal infections, now under attack as the precipitating factor in rheumatic fever, should be minimized by avoiding exposure to crowds or to family and friends with colds and sore throats, exposure to cold and rainy weather, and undue fatigue, and by the use of suitable clothing. The preventive value of immunization with streptococcal vaccines[148, 141] or filtrates[156] is unproved. They may cause severe reactions and activation of the disease.[15]

Air sanitation measures have been undertaken in order to prevent the dissemination of streptococcal and other infections through the air of relatively enclosed spaces.[104] A reduction in respiratory infections has been reported following the use of ultraviolet radiation,[124] suppression of dust by oiling of bedding, bed clothes and floors,[118] and by the dispersal of germicidal vapors (aerosols).[114]

Climatic Therapy. The reported infrequency of rheumatic fever in tropical and subtropical climates has served as rationale for the transplantation of rheumatic patients to such climates. Reports of the cessation of active rheumatic infection in patients removed to Puerto Rico have been noted (p. 703). A similar project has been conducted in Miami, Florida,[120] and the Army Air Force has set up rheumatic convalescent hospitals in areas of low rheumatic incidence for the purpose of avoiding reactivation of the disease.[66]

The practicability of such projects as a routine form of management appears very restricted. Rheumatic fever in general occurs in poor families for whom such a change of environment often imposes an excessive financial burden. The advantages appear limited in that there are recurrences upon the return

to the original environment. Recurrences may even develop despite a continued residence in the new environment. Certainly a family's economic and social security should not be uprooted in the overoptimistic hope that a brief residence in a southern climate will effect a cure or even prevent recurrence. If, however, only a moderate sacrifice is entailed, it may be justifiable to remove the patient to a southern climate during the cold and rainy seasons. In occasional instances it may even be feasible to transplant the rheumatic child to areas in which hemolytic streptococcal infections and rheumatic fever are relatively rare, and to keep him there until he is past puberty. But as a general solution of the problem of rheumatic recurrences, this is impractical and its merits unproven.

Prophylactic Salicylates. Salicylates, in daily dosage of 2 to 6 gm., have been given prophylactically to rheumatic patients for several weeks after an upper respiratory infection in an effort to prevent the recurrence of rheumatic fever.[84, 126, 31] The merits of this procedure require further evaluation.

Prophylactic Sulfonamides. The prophylactic administration of sulfonamides has been used to prevent both hemolytic streptococcal infections and the rheumatic fever which often follows in their wake. Promising results were obtained by the administration of 0.5 to 2.0 gm. daily of sulfanilamide and later sulfadiazine to children and adolescents with inactive rheumatic fever.[152, 30, 81, 151, 7] Similar mass prophylaxis with sulfonamides was reported to diminish sharply the occurrence of streptococcal infections including scarlet fever, and the incidence of subsequent rheumatic fever.[159, 29, 65]

Several disadvantages of sulfonamide prophylaxis have developed: (1) Toxic manifestations were frequent, including fever, nausea and vomiting, dermatoses and leukopenia or rarely agranulocytosis.[138] These have been diminished by the use of sulfadiazine in place of sulfanilamide and by reducing the daily dose to a maximum of 1 gm. (2) There is frequently a rapid reappearance of hemolytic streptococci in the pharynx, nasopharynx or nasal passages after discontinuation of the sulfonamides. This necessitates uninterrupted prophylactic medication throughout all or almost all of the year. (3) Most important is the development of sulfonamide-resistant strains of hemolytic streptococci, e.g., the famous type 17, which are responsible for outbreaks of pharyngitis.[45, 36] In summary, the results of sulfonamide prophylaxis to prevent rheumatic recurrences have not been sufficiently impressive, considering the risks and practical difficulties involved, to justify the universal application of this measure.

Prophylactic Penicillin. To overcome some of the objections to chemoprophylaxis with sulfonamides, penicillin has been employed for the same purpose. Goerner and associates[51] were able to eliminate hemolytic streptococci from the throats of 17 out of 18 chronic carriers of these organisms, by the intramuscular administration of a total of 1,200,000 units of penicillin over a period of ten days. However, only oral administration can be considered really practical, since the antibiotic must be administered for long periods or most of the year. There is evidence that with adequate oral doses of penicillin, hemolytic streptococci can be eliminated from the pharyngeal and nasal flora of carriers in almost all instances and the microorganisms do not recur as a rule. Furthermore, penicillin-resistance develops relatively uncommonly in hemolytic streptococci. But when a daily oral dose of only 100,000 units of penicillin was given, penicillin-resistant strains of β-streptococci developed in 82 per cent of

64 rheumatic children treated prophylactically for four months.[103] On the other hand, when 1 million units of oral penicillin were given daily for five to ten days, hemolytic streptococci were virtually eliminated from the throat and penicillin resistance avoided.[78, 135, 103, 95] As a method of rheumatic fever prophylaxis, the administration of oral penicillin is still experimental. However, the prompt administration of penicillin in adequate dosage is important when rheumatic children develop acute nasopharyngitis or tonsillar infections.

Psychotherapy. Few things are more terrifying than the sense of impending doom which comes to an individual when he learns that he is suffering from heart disease. But experience with other chronic illnesses beginning in youth, such as diabetes and tuberculosis, has demonstrated the advantages of teaching patients to understand their illness and of enlisting their valuable cooperation. It is my policy therefore to explain the disease to the patient directly, if he is sufficiently mature, or to the parents in the case of a young child. There is no need to accompany the information with a long dour face, with innumerable restrictions as to mode of living or with specific pessimistic predictions as to life expectancy.

The approach to the patient and his family depends on the severity of the heart disease encountered. If the patient is well compensated and the discovery of valvular heart disease is a mere accident of routine examination, it is wise to inform the patient of his condition and to stress the possibility of a relatively normal life span if he cooperates. When, however, there is continuous or frequently recurring low grade rheumatic activity, cardiac failure or limited cardiac reserve, not the patient but someone close to him should be made aware of the seriousness of the outlook.

Whenever the patient appears, either for follow-up examination or for incidental extracardiac complaints, so long as the heart is functioning satisfactorily, the physician should not overlook these opportunities for commenting how well the heart is behaving. Such encouragement is of prodigious value to the patient's mental outlook, while failure to comment may leave him with a sense of prolonged depression and with neurotic symptoms. Only occasionally one encounters a patient who is in no danger of a neurosis but who must be struck with the fear of imminent death in order to obtain the mildest degree of cooperation.

The well compensated rheumatic cardiac may suffer from a variety of symptoms, particularly aches and pains and abdominal distress which are really of a functional nature but which he fears may be related to his cardiac disease. Reassurance as to his cardiac status and discovery of the basis of the symptoms generally lead to their control.

A frequent and sometimes trying problem is presented by *attacks of palpitation.* These are associated with tachycardia, extrasystoles or both. Because of the presence of organic heart disease, it is difficult to avoid the conclusion that these symptoms have an organic basis. However, it must be emphasized that palpitation occurs also in normal individuals and while the diseased heart may be more susceptible to the arrhythmias, even in such a heart they may be due essentially to extracardiac factors.

I have found that palpitation and other forms of distress referred to the precordium usually respond to the following regime: Adequate sleep should be provided and long hours of work avoided. If the patient's occupation involves undue mental stress, it should be changed if possible. The bowels are regu-

lated, preferably without the use of cathartics or enemata. Smoking and the ingestion of alcoholic beverages are eliminated completely. Coffee and tea are preferably avoided, but these are rarely the cause of symptoms. The diet is important and is designated to counteract flatulence and hyperacidity. Raw fruits, salads, cucumbers, onions, cabbage, cauliflower, kohlrabi, broccoli, cheeses (except cottage and cream cheese), bran products, cold cereals, chocolates and pastries, corned meats, smoked fish and fried foods are eliminated from the diet. If there is gastric hyperchlorhydria, the patient is given frequent, bland feedings and alkaline powders. Atropine may also be useful alone or in combination with the alkaline powders. Mild sedatives are frequently useful.

It is of great value in treatment to reassure the patient as to the competence of his heart and to explain that the palpitation is probably not related to the heart disease and may occur in normal persons.

Advice on Occupation, Marriage, Pregnancy and Childbirth. The rheumatic cardiac usually reaches the chronic inactive stage of his disease at an early age. Thus he often expects from his physician advice as to the choice of a suitable occupation, and as to marriage. Married women patients want to know the dangers of pregnancy and childbirth. Unfortunately, the choice of an occupation is not a free one, but is conditioned by social and economic factors, and by chance as well as by ability and opportunity for training. To the extent that choice is possible, the occupation chosen should permit control of hours of work and working conditions. This usually means self employment either as a business proprietor or in some profession. When employed by others, the work should not entail long or irregular hours, severe physical or mental stress, or exposure to dampness, drafts, extremes or sudden changes of temperature, or undue crowding.[140] The education and cooperation of employers in the most efficient use of rheumatic cardiacs should be helpful.

The patient's question as to the advisability of marriage is usually a rhetorical one. Generally the patient comes for advice when marriage is already pending, and then he comes only for acquiescence in his decision. The physician's task can only be to evaluate the patient's cardiovascular status and to inform him as to the probable outlook in terms of that status and available limited knowledge of prognosis.

Pregnancy and *childbirth* are discussed in Chapter 47.

The Treatment of Chorea

This is essentially a problem in *nursing care*. It is important to maintain nutrition, avoid overstrain and injury, assure cleanliness of the mouth and skin and obtain as much mental and physical comfort as possible. Rest, in a bed with sideboards, is obligatory if there is marked loss of motor control. The sideboards as well as the head and foot supports should be well padded. Special attention to the patient's needs for defecation or urination is necessary, especially if the child cannot make his desires known because of speech disturbance. The nurse will look for sores, injuries, toothache, etc., which the patient cannot reveal by speech, and which may serve to exaggerate his mental and emotional irritability. Patience and encouraging assistance are invaluable in feeding the child if the all-important nutrition is to be maintained. When this is too difficult or too trying for the patient, it is wise to resort to nasal feeding.

Sedatives are useful to reduce exaggerated activity in the daytime and to obtain sleep at night.

Salicylates are often employed, but are not indicated unless there is fever or arthritis.

Numerous direct methods of treating chorea have been employed. While there have been many enthusiastic claims of cures, the constant shift to new "cures" casts suspicion on these claims. A course of treatment with *nirvanol* (sodium phenylethylhydantoin) has been extensively employed.[112, 40] Two grains (0.120 gm.) are given twice daily for children under ten; 2½ grains (0.150 gm.) twice daily for those beyond ten. This is continued for ten days to two weeks but is stopped promptly at any time during this interval if a rash or sudden pyrexia supervenes. The reaction which indicates completion of the course of treatment is characterized by the following symptoms: headache, conjunctivitis, drowsiness, cervical adenitis or a well marked morbilliform rash.

Artificial pyrexia has recently been employed both in chorea and rheumatic carditis.[146, 9, 42] The pyrexia is induced by intravenous injections of typhoid vaccine,[146, 10] or hyperthermia is obtained by the diathermy machine, the radiotherm,[8] or the hot box.[13] Their effectiveness and safety for the rheumatic patient are still sub judice. Sutton and Dodge[146] used the New York City triple typhoid vaccine containing 1000 million B. typhosus and 750 million each of B. paratyphosus A and B per cc. They begin with 0.05 to 0.1 cc. of the vaccine given intravenously and increase the dose gradually according to the patient's reaction. They try to produce fever up to 104° to 106° F. Daily treatments are given with occasional rest periods. On the average six to nine injections are administered. With the radiotherm, one to two treatments are given, the patient's temperature being raised to 106° F. and maintained at that level for two to five hours. Constant supervision is essential.

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BACTERIAL ENDOCARDITIS

Bacterial endocarditis is a disease due to bacterial infection of the valvular and mural endocardium. The causative organisms can usually be demonstrated during life by blood cultures, and post mortem by spreads of the endocardial vegetations. The clinical picture is that of a general infection (septicemia) with endocardial, embolic and local vascular symptoms of variable prominence. Detailed descriptions may be found in the publications of Osler,[131] Schottmüller,[156] Horder,[76] Billings,[9] Libman,[97] Blumer,[11] Thayer,[170] Perry[134] and Libman and Friedberg.[100]

Bacterial endocarditis is a frequent and important cardiac ailment, ranking in incidence next to arteriosclerotic, hypertensive and rheumatic heart disease. In many localities it is encountered much more frequently than cardiovascular syphilis. Its frequency in various localities depends on the frequency of rheumatic heart disease, of which it is usually a complication. Bacterial endocarditis develops in about 10 to 25 per cent of the cases of rheumatic heart disease,[31, 57] but in the series of Laws and Levine[94] it was the cause of death in as many as 29 per cent of 148 cases of rheumatic heart disease.

Bacterial endocarditis is subdivided into acute and subacute bacterial endocarditis, of which the latter is much more common. In general the cases are considered to be acute if their duration is less than six weeks and subacute if longer than that period. This division is not a sharp one because the time of onset is usually difficult to establish, and because there is considerable overlapping in the clinical, bacteriologic and pathologic features of the two forms. On the other hand, this classification is not entirely arbitrary because the acute and subacute cases are generally due to distinctly different organisms. Occasionally, organisms usually associated with the acute disease produce a subacute bacterial endocarditis and those generally associated with the latter may produce an acute bacterial endocarditis. The acute and subacute forms usually present distinct pathologic and clinical differences which justify their separation. In general, in subacute bacterial endocarditis the original focus is uncertain or practically asymptomatic and the clinical picture is due essentially to the endocardial lesions and their complications. In acute bacterial endocarditis, the endocardial infection is often secondary to a gross apparent focus (often of a surgical nature) or to some other primary disease with bacteremia, and the clinical picture of the endocarditis is dominated and obscured by the initial focus and the bacteremia. As early diagnosis and effective treatment become

more widespread, the distinction between acute and subacute bacterial endocarditis will become academic. Nomenclature will be based on the etiologic agent, e.g., Streptococcus viridans endocarditis, gonococcal endocarditis, etc.

SUBACUTE BACTERIAL ENDOCARDITIS

ETIOLOGY

Causative Organisms

In about 95 per cent of the cases of subacute bacterial endocarditis the causative organism is a nonhemolytic streptococcus. Because of the importance of bacteriology in the proper diagnosis and treatment of this disease, a brief discussion of these causative organisms is pertinent.

Classification of Streptococci. Unfortunately the classification and terminology of the nonhemolytic streptococci is in a state of flux.[139] According to their effects on blood agar plates,[164] the streptococci producing colonies surrounded by a clear zone of hemolysis are termed hemolytic or beta streptococci. This type corresponds to the long-chained Streptococcus pyogenes of former terminologies, which may cause an acute bacterial endocarditis but very rarely the subacute form. Streptococci forming colonies without a sharp clear zone of hemolysis are termed nonhemolytic streptococci and subdivided into *Streptococcus viridans or alpha* if the colony is surrounded by a zone of greenish discoloration with or without partial hemolysis, and *Streptococcus anhemolyticus or gamma* if there is neither greenish discoloration nor hemolysis around the colonies on blood agar plates.

Varieties of Nonhemolytic Streptococci. Of the nonhemolytic streptococci responsible for subacute bacterial endocarditis, the Streptococcus viridans causes about 80 per cent of the cases and gamma streptococci (sometimes called indifferent streptococci) cause about 15 per cent. The Streptococcus viridans (alpha) is the organism frequently found in the oral cavity and was therefore formerly termed the Streptococcus salivarius. Another organism of the oral cavity, termed Streptococcus mitis, is also a Streptococcus viridans.

A special group of nonhemolytic streptococci sometimes responsible for subacute bacterial endocarditis are the enterococci. These are usually of the gamma type, and because they are commonly found in the intestinal tract were formerly called Streptococcus fecalis. They have been characterized by their heat resistance (60° for thirty minutes) and by their fermentation of esculin, which is turned black. They usually appear in pairs of ovoid cocci, or occasionally in short chains. Unlike the Streptococcus viridans, the enterococcus ferments mannitol. The enterococcus is of special interest because it is often much more resistant to penicillin than the Streptococcus viridans, the more common causative organism of subacute bacterial endocarditis.

Recently Loewe, Plummer and associates[108] segregated a special nonhemolytic streptococcus which they termed Streptococcus s.b.e. and which was responsible for 40 out of 115 consecutive cases of subacute bacterial endocarditis. This organism produced greening on blood agar in twenty-four hours, hydrolyzed arginine in forty-eight hours, fermented inulin in a week and did not produce large mucoid colonies on sucrose agar. These observers believed that this group of nonhemolytic streptococci was more resistant to penicillin than other groups and that a higher percentage of complications and fatalities

occurred in cases due to "Streptococcus s.b.e." That the Streptococcus s.b.e. forms a distinct serologic group has been confirmed.[155a] However, although it is slightly more resistant to penicillin in vitro than most of the other causative strains of Streptococcus viridans, in our experience it has not been found to produce a different clinical picture or a higher incidence of complications or recurrences.

These various descriptive characteristics, purported to distinguish the different nonhemolytic streptococci, have not served to segregate sharply specific groups. Considerable study has recently been devoted to their serologic classification on the basis of type specific carbohydrate antigenic substances.[165, 186] It has been shown that the enterococci possess the specific carbohydrate of the Group D streptococci of Lancefield.[92] On the other hand the alpha streptococci (viridans) probably fall into a number of species or types, some of which belong to Group D. Increasing knowledge of the nonhemolytic streptococci may enhance our skill in utilizing the various antibiotics to control subacute bacterial endocarditis.

The nonhemolytic streptococci are characterized by a low degree of virulence in contrast with the microorganisms usually responsible for acute bacterial endocarditis. The former are generally common saprophytic inhabitants of the mouth, upper respiratory and gastrointestinal tract and possess a low pathogenicity for laboratory animals. The usual habitat of the Streptococcus viridans in the nasopharynx and oropharynx, and often in infected tonsils and apices of infected teeth, suggests that most of the cases of subacute bacterial endocarditis result following accidental passage of this organism from the oral or pharyngeal cavity into the blood stream. Similarly the enterococcus is a microorganism of relatively low virulence and is a common inhabitant of the intestinal tract. The latter may be the portal of entry of the enterococcus into the blood stream in some cases of subacute bacterial endocarditis, but not uncommonly the enterococcus causing a bacterial endocarditis apparently arises in the genitourinary tract. Enterococcus endocarditis is not distinctive clinically from the subacute bacterial endocarditis due to the Streptococcus viridans.[163]

Uncommon Causative Organisms. About 5 per cent, or at most 10 per cent, of the cases of subacute bacterial endocarditis are due to a great variety of microorganisms other than the nonhemolytic streptococci. These fall into two groups: (1) microorganisms which are common saprophytic inhabitants of the human body but which by chance invade the blood stream and may produce bacterial endocarditis if they find conditions favorable for localization and growth on the cardiac valves; (2) microorganisms usually of greater pathogenicity, which are not normal human inhabitants but which may be introduced from without and cause a more or less characteristic disease with bacteremia; occasionally and incidentally this bacteremia is complicated by a bacterial endocarditis. The latter group of microorganisms may cause either an acute or subacute endocarditis.

(1) Among the former group of infrequent causative organisms of subacute bacterial endocarditis are the *Hemophilus influenza*[138] and parinfluenza,[28] the gram-negative *Neisseria pharyngis group*[184] (N. pharyngis sicca, N. catarrhalis and N. flavus), and the *Corynebacteria* (diphtheroids). Like the nonhemolytic streptococci most of these are common saprophytes of the upper respiratory tract and oral cavity. Diphtheroids must be distinguished from a diphtheroid phase of a nonhemolytic streptococcus.

(2) Among the second group of infrequent causative organisms of subacute bacterial endocarditis the *N. gonococcus* is the most frequent,[170, 190, 32] corresponding to the relative frequency of gonorrhea and its complications. With careful bacteriologic technic a gonococcal bacteremia can be demonstrated more often than is generally recognized.[52] Because of cultural difficulties the gonococcal etiology of a bacterial endocarditis is usually overlooked during life.[32] The *meningococcus* may cause an acute or subacute bacterial endocarditis as a complication of meningococcemia with or without meningitis.[125, 48] Subacute bacterial endocarditis has been reported with each of the varieties of organisms responsible for brucellosis (undulant fever), i.e., *Brucella abortus, melitensis and suis.*[168, 36]

Subacute or acute bacterial endocarditis, with a tendency to localize on the tricuspid valve, has been caused by the *Staphylococcus albus or aureus* following intravenous injections of heroin by addicts,[78] but subacute Staphylococcus albus or aureus endocarditis has also arisen without such apparent portal of entry.[76, 170, 166] Staphylococci may be part of the normal bacteriologic flora of the nose. Joachim and Polayes[80] also observed the development of subacute bacterial endocarditis due to a yeast (*Candida or Monilia parakrusei*) in a morphine addict who had injected intravenously a contaminated solution of morphine. Similar cases of mycotic endocarditis were documented by Wikler and his associates.[187] There are other reports of subacute bacterial endocarditis due to higher bacteria, yeasts or fungi,[133, 6] including cases due to Actinomycosis bovis[177, 24, 183] and Histoplasma capsulatum.[16] A variety of special media and technics may be necessary to isolate the causative organisms in these cases. The Erysipelothrix rhusiopathiae of swine erysipelas may cause erysipeloid and a complicating subacute bacterial endocarditis in humans who handle infected fish or who make buttons of fish bones.[148] Rat-bite fever with complicating subacute bacterial endocarditis may be caused either by the Streptobacillus moniliformis[10, 112] or by the Spirillum minus.[74]

Isolated instances of subacute bacterial endocarditis have been caused by almost any microorganism which invades the blood stream, including E. coli,[51] B. proteus or Pseudomonas aeruginosa (B. pyocyaneus[119]) and B. friedlander (Klebsiella pneumoniae), following infections or manipulations of the genitourinary tract. These microorganisms are resistant to penicillin but are usually sensitive to streptomycin, aureomycin or chloromycetin. For this reason it is important to identify and distinguish them from the more usual causes of subacute bacterial endocarditis. Rarely bacilli of the subtilis group, salmonella, clostridia, Micrococcus tetragenus, Diplococcus mucosus, Diplococcus crassus, B. necrophorus (B. fusiformis), Doederlein's bacillus or C. diphtheriae[18] may cause subacute bacterial endocarditis. The tubercle bacillus attacks the endocardium rarely, but only as part of a generalized miliary tuberculosis[4] or by extension of pericardial and myocardial tuberculosis. An anaerobic streptococcus or staphylococcus may be responsible.[129]

Mixed Infections and Reinfections. Mixed infections occur occasionally and may present difficulties in the interpretation and treatment of a given case.[130] I have seen combined infections with Streptococcus viridans and the pneumococcus, S. viridans and Staphylococcus aureus, S. viridans and diphtheroids, the Staphylococcus aureus and the enterococcus, Staphylococcus albus and enterococcus. Combined infection with S. viridans and H. parainfluenzae was

reported by Olinger.[128] One of the organisms may be rapidly eradicated by antibiotic therapy but the disease may continue because of persistence of the other causative organism which requires larger dosage, more prolonged treatment or streptomycin or other antibiotics instead of penicillin.

There are already numerous instances of reinfection causing subacute bacterial endocarditis following cure with penicillin. That the new attack is due to a fresh infection is certain when the latter attack is caused by a different organism from the one responsible for the former. However, reinfection with the same species of organism rather than a relapse may be assumed as probable if three months elapse after all clinical and laboratory evidence of the infection has disappeared. The more conservative demand a free interval of a year.[142] In one patient I have seen a bacterial endocarditis due to Staphylococcus aureus cured by penicillin, a second attack one year later due to a microaerophilic streptococcus likewise cured by penicillin, and a third attack six months later due to a Streptococcus viridans from which he also recovered.

Predisposing Factors

Previous Valvular Disease. *Rheumatic Cardiovalvular Disease.* Subacute bacterial endocarditis usually involves a heart with an acquired valvular defect due to rheumatic fever. Even before 1900 Kelynack[86] had found bacterial endocarditis often associated with preexisting valvular disease and shortly afterward Glynn[62] emphasized this relationship in a study of 61 cases of bacterial endocarditis in which there was a rheumatic history in 60 per cent. In my postmortem observations, evidence of rheumatic heart disease was present in 79 per cent of 100 consecutive cases of subacute bacterial endocarditis. A similar incidence of underlying rheumatic cardiovalvular disease was noted by Seabury,[158] while Christian[21] recorded 134 instances (89.3 per cent) of rheumatic heart disease in 150 consecutive cases of subacute bacterial endocarditis. Subacute bacterial endocarditis may develop in hearts with active or inactive rheumatic disease. Aschoff bodies have been encountered in about 40 per cent of the hearts with subacute bacterial endocarditis.[178, 67]

It is the valvular defect as such and not the rheumatic fever which accounts for the frequency of complicating bacterial endocarditis. It is apparent that the identical clinical picture can follow infection of the valves by a host of different bacteria and that underlying rheumatic disease may be entirely absent. Von Glahn and Pappenheimer[178] thought that active rheumatic vegetations were necessary for the bacterial endocarditis, but this concept is invalidated by the cases in which bacterial endocarditis complicates congenital cardiac defects or occurs on normal valves. Rheumatic fever is the chief predisposing cause of subacute bacterial endocarditis only because it is the predominant cause of valvular deformities.

Bicuspid Aortic Valve. Of special interest is the association of subacute bacterial endocarditis with bicuspid aortic valves.[1] Lewis and Grant[95] noted that more than 23 per cent of males who reached adult life with this abnormality died of subacute bacterial endocarditis. Furthermore, in a consecutive series of 31 cases of subacute bacterial endocarditis, a "congenital" bicuspid aortic valve was found in 26 per cent. However, in a more recent study from the same hospital, Wauchope[182] found that only 6 (11.5 per cent) of 52 cases with aortic bicuspid valves developed subacute bacterial endocarditis and 2 of these

6 had other congenital abnormalities as well. Wauchope also observed that there were only 5 instances of bicuspid aortic valves among 95 cases of subacute bacterial endocarditis.

While Lewis and Grant[95] and Abbott[1] considered the bicuspid aortic valve to be a congenital malformation, Gross[66] presented evidence that the majority of bicuspid aortic valves are actually deformed cusps due to healed rheumatic infection. Koletsky[89] arrived at a similar conclusion as a result of his studies of 50 bicuspid aortic valves, 40 of which were rheumatic and 10 of congenital origin. In 8 of the 50 (16 per cent) there was a superimposed bacterial endocarditis—acute or subacute. According to Koletsky, bicuspid aortic valves are encountered in 6 to 12 per cent of cases of bacterial endocarditis.

Syphilitic Aortic Valvular Disease. Occasionally bacterial endocarditis originates in valves deformed by syphilis.[15, 191] In Christian's[21] series of 150 cases of subacute bacterial endocarditis there was 1 instance of syphilitic aortitis and 3 of combined rheumatic and syphilitic cardiovalvular disease. Koletsky[90] also stressed the simultaneous presence of rheumatic disease in most instances of combined bacterial endocarditis and syphilitic cardiovascular disease and doubted the significance of syphilis as a predisposing factor. The infrequency of bacterial endocarditis in syphilitic aortic insufficiency may be due at least in part to the relative infrequency of syphilitic as compared with rheumatic valvular disease. There is also a difference in anatomic lesions for in syphilis there is neither a true valvulitis nor verrucous alteration to trap bacteria as in rheumatic fever.

Congenital Cardiovascular Abnormalities. Congenital cardiovascular anomalies are next in importance to rheumatic deformities in predisposing to subacute bacterial endocarditis. Cardiovascular anomalies are present in 10 to 20 per cent of the latter cases. Conversely Gelfman and Levine[58] noted that bacterial endocarditis occurred in 6.5 per cent of all cases of congenital cardiac defects and in 16.5 per cent of those patients who survived the age of two.

Of the grosser congenital cardiac lesions the patent ductus arteriosus is most frequently involved, in my experience. The vegetations produce an endarteritis of the pulmonary artery and of the ductus.[59] According to Abbott,[1] the interventricular septal defect is more often complicated by bacterial endocarditis, and similarly Gelfman and Levine[58] found bacterial endocarditis in 42 per cent of the cases of ventricular septal defects as compared with 28.6 per cent of the cases of patent ductus. However, the much higher incidence of the latter anomaly accounts for a significantly greater absolute number of cases of bacterial endocarditis with patent ductus arteriosus. The relation of bacterial endocarditis to bicuspid aortic valves has been discussed. Jouve[82] believes that pulmonary stenosis is the congenital cardiac lesion most frequently complicated by bacterial endocarditis; this may occur in cases of tetralogy of Fallot or in uncomplicated pulmonic stenosis.

Bacterial endocarditis complicates a congenital subaortic stenosis more frequently than recorded figures indicate.[180] Bacterial vegetations of the aorta are not uncommon in cases of congenital coarctation. Properly speaking these are instances of subacute bacterial aortitis but the clinical picture and course are essentially identical with that of subacute bacterial endocarditis. Not infrequently subaortic stenosis, coarctation and bicuspid aortic valve are all present in the same case. In cases of interatrial septal defects there is a striking rarity

of subacute bacterial endocarditis even though mitral stenosis is usually associated with the septal defect.

Arteriovenous Aneurysm. Rarely a traumatic arteriovenous aneurysm is complicated by a bacterial endarteritis similar to that complicating a patent ductus arteriosus. The bacterial endarteritis usually is further complicated by a bacterial endocarditis if antibiotic or surgical treatment (p. 803) is not instituted.

Operative Procedures—Dental Extraction and Tonsillectomy. It has been repeatedly noted that subacute bacterial endocarditis develops following the extraction of a tooth or the removal of tonsils, especially in subjects with rheumatic or congenital cardiac defects.[176, 185, 116] The Streptococcus viridans is the common organism found in infected tonsils and dental apical abscesses and may be thrust into the blood stream by the operative procedure. Okell and Elliott[127] observed a transient bacteremia (preponderantly Streptococcus viridans) following dental extraction in 72 per cent of patients with septic mouths and in 32 per cent of subjects without obvious infection of the oral cavity. Similar observations have been made by others.[135] Burket and Burn[19] demonstrated the dental origin of the bacteremia by implanting a non-pathogen (Serratia marcescens) about the teeth and recovering it from the blood stream following dental extraction. Transient bacteremias have also been observed following tonsillectomy.[49, 45] Such transitory bacteremias are rarely significant in the normal individual, but in persons with cardiovascular abnormalities, the microorganisms may localize about the endocardial defects and set up a bacterial endocarditis. It is also probable that less decisive traumata than extraction of teeth or tonsillectomy, e.g., brushing or filling of teeth, chewing, etc., may initiate transient bacteremias, especially in patients with dental or gingival infection.

Among operative procedures, those on the genitourinary tract (cystotomy, prostatectomy, transurethral resection and even cystoscopy and catheterization) have in my experience been responsible for inducing not only transient bacterial invasion of the blood stream but also subacute bacterial endocarditis. The causative organism in these cases is usually the enterococcus, the Friedländer bacillus (Klebsiella pneumoniae), Escherichia coli, Pseudomonas aeruginosa (B. pyocyaneus) or rarely B. proteus. Induced abortions have several times in my experience accounted for the development of acute or subacute bacterial endocarditis. Anaerobic streptococci, enterococci and Staphylococcus aureus have been the usual causative organisms but in one case there was a mixed infection with enterococcus and Staphylococcus aureus. The possibility that infections of the intestinal tract, especially those associated with diarrhea, or even drastic purgation or enemata may precipitate bacteremia and bacterial endocarditis is not far-fetched. Enterococcic infections are particularly apt to have their portal of entry in the intestine.

Respiratory Infections. Because the Streptococcus viridans and Hemophilus influenzal organisms, the common causative agents of subacute bacterial endocarditis, are frequent normal inhabitants of the upper respiratory tract, their invasion of the blood stream and implantation on deformed valves may be facilitated during an upper respiratory infection. Infections of the upper respiratory tract together with dental infections and tonsillectomy have been indicted as precipitating factors in over 70 per cent of cases of subacute bacterial

endocarditis.[181, 137, 179] In some instances, however, the patient reports the disease to have followed a "cold" or the "grippe" when actually the so-called grippal episode was itself the manifestation of subacute bacterial endocarditis.

Pregnancy and Puerperium. Subacute bacterial endocarditis may have its onset during pregnancy or shortly after childbirth.[14, 33] During pregnancy the relationship is probably coincidental. However, childbirth itself may be associated with transient bacteremia, especially when there is pelvic inflammatory disease.

Age and Sex. The highest incidence is in the third decade, and cases occur commonly also in the second and fourth decades. But subacute bacterial endocarditis may occur at almost any age from early childhood to late in life. I have seen it in a man of seventy-four. It is perhaps wise to stress the occurrence of bacterial endocarditis in the elderly because the disease may be atypical and usually overlooked in these individuals.[192] Many cases have been reported in children but rarely under the age of five.

There is a somewhat higher incidence in males than in females.[100, 11, 158]

PATHOGENESIS

Portal of Infection. The development of subacute bacterial endocarditis is dependent on the entrance of microorganisms into the blood stream. Because the causative organisms, particularly the Streptococcus viridans, are common inhabitants of the mouth and upper respiratory tract, the portal of entry is believed to be located in infected foci about the teeth, tonsils, nasopharynx and oropharynx. The demonstration of transient bacteremias following dental extractions and tonsillectomy and the clinical observations that bacterial endocarditis often follows extraction of teeth or tonsillectomy support this localization of the portal of entry. The portal of entry may also be located in the intestinal or biliary tract in cases of enterococcus (Streptococcus fecalis) endocarditis or in the urinary or genital tract.

Experimental Endocarditis. Bacterial endocarditis has been produced experimentally by the intravenous injection of a variety of organisms. The disease may be induced by repeated intravenous injection of nonhemolytic streptococci from cases of subacute bacterial endocarditis or other human sources.[99, 41] But as a rule experimental bacterial endocarditis is produced more readily if a cardiac valve is damaged first, if the bacteria are injected together with coarse particles which aid valvular implantation, or if casein, pituitrin or other substances are first injected, presumably to modify the immunologic response or alter the surface of the valve in such a manner as to promote bacterial adhesion.[122]

These experimental data correspond to clinical observations that previous valvular damage and bacteremia are the two main factors responsible for the development of subacute bacterial endocarditis but that the former is not essential. The frequency with which rheumatic cardiovalvular disease precedes subacute bacterial endocarditis suggests that immunologic factors are of some significance, but the bacterial endocarditis may develop on normal valves or in hearts with congenital anomalies in which immunologic alterations are not apparently concerned.

Method of Implantation of Bacteria on Valves. It is probable that the bacteremia which initiates subacute bacterial endocarditis is usually of very brief duration and occurs either in the course of ordinary physiologic activities,

as a result of infections of the oral cavity, upper respiratory, intestinal or genitourinary tracts, or because of operative procedures in these regions. Occasionally the responsible bacteremia is more persistent and a part of a general infection (undulant fever, gonococcemia or meningococcemia).

The circulating bacteria are implanted on valves, mural endocardium or vascular intima by way of the general blood stream. Platelet thrombi on previously damaged valves or recent valvular vegetations aid in the localization of the infection.[65, 68] The development of a fibrin wall may provide a medium of growth at the same time that it protects against bactericidal substances.[55]

But the localization and implantation of bacteria are determined chiefly by mechanical factors of impact and perhaps contact.[64, 2] The bacteria appear to settle and multiply wherever they are sprayed forcefully on a receptive area. This is often determined by changes in pressure dynamics and stream flow induced by valvular stenoses and insufficiencies or by cardiovascular shunts. In hearts with a patent ventricular septum the endocarditis appears on the endocardium of the pulmonary conus of the right ventricle opposite the septal defect through which a stream of bacteria-laden blood is sprayed against the opposite wall. In cases of patent ductus the endarteritis begins in the pulmonary artery as if it were forcibly sprayed there through the open ductus. In these instances as in valves altered by rheumatic fever, tension changes in the mural endocardium or vascular intima may favor bacterial implantation. However, implantation may occur on apparently normal valvular or mural endocardium but this is more likely in the acute bacterial forms of endocarditis due to more virulent organisms and more persistent bacteremias.

PATHOLOGY

The Heart

Valves and Vegetations. The most striking feature is the presence of *vegetations* on the valves and on the parietal endocardium. These may be discrete like rheumatic verrucae but are usually larger. They may also be flat and granular or occasionally exuberant fungating or cauliflower vegetations. Rarely the latter are large enough to occlude a valvular orifice. The two important characteristics of these vegetations are: (a) the presence of bacteria which are constantly swept into the blood stream and which are responsible for the fever, toxemia and bacteremia of the disease, and (b) their friability, which accounts for the fragmentation of particles which are disseminated as embolic bacterial masses.

Microscopically the vegetations have a broad base of altered, degenerated valvular substance with blood platelet thrombi, accumulations of bacterial masses, all overlaid by a fibrin and erythrocyte coating. Sometimes the vegetation has a characteristic appearance resembling necrotic liver cords.[67] Polymorphonuclear leukocytes, which abound in acute bacterial vegetations, are few or absent in the subacute cases. The underlying valvular cusp is the site of a diffuse destructive process with an inflammatory exudate of lymphocytes, mononuclear cells and some polymorphonuclear leukocytes. Sometimes there is a striking infiltration of large mononuclear cells, consisting of histiocytes and fibroblasts.

Localization of Vegetations. The vegetations are situated predominantly on

the left side of the heart except when there is a congenital communication between the two sides. The vegetations are localized chiefly to the valvular leaflets, the mitral being affected in about 80 per cent of the cases, the aortic in 60 per cent, both in 40 per cent. The aortic valve is most likely to be involved in cases of primary bacterial endocarditis, i. e., without antecedent disease. The pulmonic valve is occasionally affected, perhaps with more than casual frequency in the gonococcal cases. The tricuspid valve may be affected simultaneously with the aortic or mitral[101] but it seems to have been the site of predilection in cases of Staphylococcus albus and aureus endocarditis induced by intravenous injection of contaminated heroin. In one case of interatrial defect which I observed, the tricuspid valve was the only one infected with bacterial vegetations.

The vegetations may also be situated on the chordae tendineae or on the mural endocardium, especially of the left atrium or left ventricle and occasionally on the interventricular septum or pulmonary conus of the right ventricle or on vascular intima. Bacterial involvement of the chordae may lead to necrosis and rupture and their loose ends may be seen dangling unattached. The aortic valvular vegetations frequently spread by contiguity along the ventricular endocardium and produce "moth-eaten" bacterial lesions on the ventricular surface of the anterior mitral cusp. They may also extend to the distal surfaces of the aortic cusps and involve the sinuses of Valsalva and the adjacent aortic intima. In the left atrium bacterial vegetations may produce a characteristic nodular plaque-like lesion with a coarse sharkskin appearance,[67] often superimposed on a previous rheumatic auricular lesion.

Local Complications of Bacterial Vegetations. The destructive effect of the bacterial vegetative lesions leads to *complications* including *mycotic aneurysms, perforations of valve cusps, rupture of chordae tendineae, perforations of interventricular septa or sinus of Valsalva.*

Necrosis of valvular substance may lead to local ulceration, aneurysmal pouches or occasionally to perforation of cusps.[152] Bacterial endocarditis may increase the anatomic deformity and functional impairment previously present or initiate a valvular insufficiency or rarely a stenosis. I have several times observed ulceration of a mycotic aneurysm at the base of the aortic valve extend into the pericardial space between the roots of the aorta and pulmonary artery and produce a clinically apparent purulent pericarditis. Bacterial necrosis of the sinus of Valsalva may lead to aneurysm formation and occasionally to perforation into the right atrium or right ventricle with characteristic clinical symptoms and signs of a communication between two vessels or chambers of different pressures. Rarely aortic and very rarely tricuspid vegetations may burrow into the subjacent myocardium and produce a perforation of the interventricular septum or septum fibrosum.

Healing of Vegetations. Healing of vegetations of subacute bacterial endocarditis were noted by Harbitz,[71] Osler[131] and others, and carefully studied by Libman[98] and by Gross and Fried.[67] In recent years healed lesions have been noted at various periods following bacterial sterilization by means of penicillin, when death resulted from some cause other than persistent infection.[141, 118, 81] Healing begins early in the deeper parts of the vegetation and is characterized by disappearance of the valvular inflammatory reaction and bacteria, marked capillarization of the subjacent valve and a fibroblastic reaction. The dilated capillaries may communicate with the cardiac chambers and produce a char-

acteristic "spongy" lesion consisting of wide anastomosing cavernous channels. The fibroblastic reaction leads to partial or complete organization and hyalinization of the vegetations with or without calcification. If bacteria are present they lose their staining quality and cannot be cultured. Eventually the small remnant of the hyalinized and fibrotic vegetation becomes covered with an endothelial process. In the penicillin-treated cases complete healing occurs in about three months after clinical control of the infection.

Myocardial Lesions. Interest in myocardial lesions has been heightened because of the frequency of cardiac failure despite control of the bacterial infection by antibiotics. However, the visible lesions appear relatively insignificant in extent and severity although they occur with great frequency.[39, 17]

Two types of myocardial lesions may be noted: (a) vascular lesions consisting of bacterial embolization of arterioles and capillaries, necrosis of the walls of these small vessels, and surrounding inflammatory reactions; (b) extravascular lesions characterized chiefly by minute infarctions due to the above vascular lesions, and foci of polymorphonuclear leukocytes or mononuclear cells. Perivascular fibrosis and organization of minute infarcts are common. Small foreign body granulomata surrounding a central deposit of calcium (embolic) have been described in fatal cases treated with sulfonamides and penicillin.[151] Suppurative lesions are uncommon. The so-called Bracht-Wächter[13] lesions are focal collections of lymphocytic and mononuclear cells. They are not characteristic and are of dubious significance. Occasionally bacterial embolization involves the larger coronary arteries[150, 132] and may produce gross myocardial infarction or sudden death. Not infrequently there are Aschoff bodies and other lesions due to coexisting rheumatic myocarditis.

Pericardial Lesions. Pericardial involvement is uncommon in subacute bacterial endocarditis but there may be lesions of a previous or concomitant rheumatic inflammation. Occasionally a diffuse pericarditis is due to an associated pneumonia or complicating uremia. A specific gross suppurative pericarditis may, however, be due to extension of the bacterial infection from an aortic valve and sinus of Valsalva to the pericardial wedge between the aorta and pulmonary artery. In one such case I observed 500 cc. of serosanguineous pericardial fluid.

Kidney

The renal lesions are of three types: (1) focal "embolic" glomerulonephritis, (2) diffuse glomerulonephritis and (3) infarcts. Grossly the kidney may present diffuse petechial hemorrhages which produce the so-called "flea-bitten" appearance[76] and depressed, yellowish sharply demarcated areas of infarction.

(1) The *focal embolic glomerulonephritis* (the Löhlein-Baehr) lesion was first described by Löhlein[110] and studied in detail by Baehr,[3] who observed it in 23 of 25 cases of subacute bacterial endocarditis due to the Streptococcus viridans. It may also occur in cases due to the H. influenzae. In subacute bacterial endocarditis due to the gonococcus or other organisms, there is usually an intracapillary glomerulitis or a diffuse glomerulonephritis.

Microscopically, the feature of the lesion is the necrosis of only a portion of glomerular vessel wall and the presence of a fibrinoid plug in the lumen of the corresponding glomerular branch.[22] The lesion has generally been regarded as embolic but it is probable that local vascular inflammation and closure play a role.[26] The swollen, necrotic portion of glomerulus becomes granular,

undergoes hyalinization and organization, and becomes adherent to the parietal layer of Bowman's capsule or subjacent interstitial tissue, its sides being covered by a reflection of the epithelium from Bowman's capsule. A characteristic pyramidal or wedge-shaped lesion is produced. Few or many glomeruli may be involved. When numerous glomeruli are involved, renal insufficiency results. In the bacteria-free stage only the healed hyaline (fibrous) form of this lesion is observed.[3]

(2) *Acute or subacute glomerulonephritis* was formerly described as infrequent in the active stage of Streptococcus viridans endocarditis, but was encountered commonly in the cases due to the gonococcus or pyogenic organisms. According to Christian[21] a diffuse proliferative glomerulonephritis was encountered in 80 per cent of the kidneys of 61 cases of subacute bacterial endocarditis which he studied. A diffuse glomerulonephritis was common in the bacteria-free cases described by Libman[98] and in cases of healing by penicillin.[81]

(3) *Infarcts* occur in about 90 per cent of untreated cases but are seen uncommonly when treatment is instituted relatively early. One or more infarcts may be present. They are generally bland, but in the cases due to the enterococcus purulent infarcts have been noted.

Spleen

The spleen is almost invariably enlarged, sometimes remarkably so. The usual weight is between 200 and 500 gm., but I have seen spleens over 600 gm. independent of other splenic disease. The spleen contains one or more anemic infarcts in 40 to 60 per cent of the cases. Suppuration occurs rarely. A perisplenitis with adhesion to the diaphragm may be associated. On section, the spleen presents the picture of a subacute or chronic splenic tumor. The malpighian bodies are frequently enlarged and prominent and, in the bacteria-free stage, may be visible as grayish punctate dots which give the spleen a characteristic aspect.

Microscopically there is hyperplasia of the lymphoid follicles with conspicuous secondary follicles. There is a considerable proliferation of the reticulum cells and occasionally of the sinus endothelium.[88] In the red pulp the granulocytes are overshadowed by lymphocytes, plasma cells and free histiocytes showing phagocytosis. The intersinusoidal cords of Billroth are widened. There may be foci of necrosis of the reticulum or of the center of the follicles as well as mononuclear cellular collections. Focal or diffuse fibrosis of the fibrillar reticulum probably represents a healing or late stage of the disease. Jouve[82] has also described a sclerosis of the lymphoid follicles and splenic tissues.

Central Nervous System

Lesions of the brain are frequent and widespread in uncontrolled cases.[37] There is often a diffuse meningoencephalitis due to disseminated bacterial embolization of arterioles and capillaries.[87, 173] Local closure may also occur secondary to an arteritis and intimal proliferation, with or without thrombosis. There is a diffuse or perivascular proliferation of micro- and macroglial cells and of astrocytes without polymorphonuclear cells or lymphocytes. Ganglion cells undergo ischemic degeneration. The meningoencephalitis may involve the cerebrum, cerebellum or cerebral ganglia. Occasionally the spinal cord is involved in a similar process and a funicular myelosis has been described.

Embolic lesions of the large cerebral arteries are common in fatal cases. Bacterial emboli lead to mycotic aneurysms and thrombosis. Cerebral, intraventricular or subarachnoid hemorrhage may result from rupture of a mycotic aneurysm, while encephalomalacia is a consequence of vascular (embolic) occlusion. Occasionally small or large cerebral abscesses are encountered, probably due to autolysis with secondary polymorphonuclear invasion of the infarcted areas.

Liver

The liver is considerably enlarged and engorged. This is due essentially to chronic passive congestion, which is seen in most fatal cases. In addition there is fatty infiltration and focal necrosis. There may be enlargement and desquamation of the Kupffer cells and focal accumulations of histiocytes.[25]

Lungs

Congestion, pulmonary emboli and infarctions, and bronchopneumonia may be encountered. Less often there are pleural effusions or hemorrhages.

Bone Marrow

There may be considerable regeneration in both the active and bacteria-free stages.

Arterial Lesions. Mycotic Aneurysms

Arterial lesions consist of embolization or arteritis. Bacterial emboli affect the large or small vessels of the brain, the extremities, the spleen, the kidney, the lungs, or of the hepatic or gastrointestinal tracts. Embolization of the lung may arise independently from venous thrombi in the lower extremities or from bacterial vegetations on the right side of the heart in congenital cardiac lesions or endocarditis of the tricuspid or pulmonic valves. Vascular occlusion results in infarction or gangrene.

Bacterial embolization also results in destruction of portions of a vessel wall with weakening of its structure and the formation of so-called mycotic (bacterial) aneurysms.[169] Most probably necrosis of the wall is secondary to infected emboli which arrive by way of the vasa vasorum and not by direct implantation on the intimal surface with secondary growth and extension.

Many of the cutaneous lesions, formerly considered the result of vascular embolization, are probably due to local (toxic? or allergic?) inflammatory changes in the walls of capillaries or arterioles. Thus the Osler node is essentially a vascular lesion, in which one or more arterioles are occluded by intense intimal proliferation.[115, 96, 26] Neighboring capillaries and arterioles show endothelial proliferation and desquamation, thrombosis or necrosis. There is a perivascular inflammation of polymorphonuclear leukocytes and histiocytes, and a diffuse cellular infiltration in the dermis and about the sebaceous glands and nerve endings. The white-centered petechiae in the skin and the so-called focal "embolic" glomerular lesion may also be due to local vascular inflammation rather than to embolization.

CLINICAL FEATURES

Mode of Onset and General Course

The onset is usually insidious. Often the patient is known to have a rheumatic or congenital cardiac defect from which he has suffered little or not at all. Most

frequently there is only fatigability, weakness or lassitude, anorexia and low grade fever. Moderate frontal headache often accompanies the fever. A considerable loss of weight may be noted. Fever, associated with joint and muscle pains, is frequently suggestive of an attack of "grippe." A careful review of the patient's history sometimes reveals a respiratory or other febrile infection from which the patient seemed to recover but never quite to a state of good health or complete apyrexia. Occasionally the patient suffers an acute rheumatic recurrence with fever and arthritis which merges imperceptibly into a complicating bacterial endocarditis. Or symptoms of the disease develop insidiously after a tooth extraction, tonsillectomy or childbirth. Symptoms of heart failure are occasionally the first evidences of the disease. Almost any other symptom of the disease may be the first manifestation, but urinary, cerebral and digestive disturbances may be particularly mentioned.

Occasionally the onset is acute, due generally to an embolic thrust in a cerebral, abdominal or peripheral vessel. Thus hemiplegias, local paralysis of an extremity, blindness due to embolism of the retinal vessel, sharp pain in the abdomen or loin due to splenic or renal infarction may suddenly reveal the presence of a bacterial endocarditis in an apparently well person. I recently observed a sixty year old woman in whom the first symptom was aphasia without paralysis, which developed while she was in the subway on her way to work. Because of her age the aphasia was thought to be due to arteriosclerotic cerebral thrombosis and she was admitted to the neurologic service. The true nature of the disease was recognized upon the discovery of mitral stenosis and low grade fever. Toone,[173] Seabury[158] and others have called attention to the relative frequency with which patients with subacute bacterial endocarditis are admitted to the neurologic service of a hospital because of cerebral manifestations at the onset.

The onset may also occur acutely with chills and high fever.

The further course of the disease is variable and depends essentially on the speed with which adequate treatment is instituted or serious embolic complications occur. In the absence of such treatment or complications the patient runs a prolonged subfebrile course with progressive weakness and anemia. Eventually if untreated or if treatment is unsuccessful death results from cardiac failure, a cerebral accident, uremia or an intercurrent infection. The duration is less than a month or two when the course is abbreviated by an embolic lesion with resulting cerebral or subarachnoid hemorrhage or when the clinical picture is that of an acute septicemia. Usually there are repeated evidences of embolization and numerous organs are involved before the fatal complication occurs. During this period the patient may have periods of apyrexia and even of tolerable comfort.

Symptoms and Signs

These may be classified into three groups: (1) general or toxemic; (2) embolic and vascular; (3) cardiac. However, since successful treatment in almost 100 per cent of cases should follow early diagnosis after only the symptoms of onset have appeared, I am hopeful that the full clinical picture as described below will be seen with increasing rarity.

1. General or Toxemic Symptoms. The general symptoms result from the toxemia of the bacterial infection. Fever is the most constant. It may be con-

tinuous, remittent, intermittent or completely irregular. It is uncommon for the temperature to rise above 103°, the usual range being between 100° and 102° F. Periods of apyrexia or of subfebrile temperature for weeks at a time are occasionally observed. Chilly sensations are not uncommon. Shaking chills occur occasionally. There may be profuse sweats. In patients who suffer chills the temperature is apt to be higher than that described above. It may reach 104° to 105° F. with sharp septic swings. Headache is common. Often in uncomplicated cases frontal headaches associated with an afternoon rise in temperature are the only symptoms.

Progressive anemia is a characteristic feature. It is occasionally the most striking symptom and the one which brings the patient for medical care. Certain other symptoms are due partly to the fever and toxemia and partly to the anemia. These include weakness, breathlessness and easy fatigability. Tenderness of the sternum and other bones may be associated with the anemia and toxemia.

2. Embolic and Vascular Manifestations. The embolic symptoms are more significant for diagnosis and are the specific evidences of this disease. Seabury's[158] review of the clinical history of 165 cases of subacute bacterial endocarditis disclosed that embolization occurred at the onset in 6.7 per cent. But as a rule embolization occurs later, when the disease is fairly advanced. Only closures and aneurysms of large vessels with resulting infarctions of organs, paralysis of extremities, or cerebral accidents can be definitely included under this heading. Other symptoms, whose embolic nature is not certain, are very helpful in the diagnosis and include white-centered petechiae and Osler nodes. The latter may produce painful fingers or toes which are sometimes the earliest symptom or chief complaint.

3. Cardiac Signs. The cardiac signs are essentially those indicating a valvular lesion or a congenital cardiovascular deformity. Usually there are murmurs and other signs of mitral stenosis or aortic insufficiency due to known rheumatic infection. There may be signs of a patent ductus arteriosus, a ventricular septal defect, subaortic stenosis or a coarctation of the aorta. Sometimes there are changes in the character and sites of these murmurs or new murmurs appear during observation of the patient.[6a] Occasionally a new rasping murmur is observed with dramatic suddenness, due to a rupture of a chorda tendinea or perforation of a valve cusp. I have repeatedly observed the development of the characteristic signs of aortic insufficiency in persons with subacute bacterial endocarditis in whom the valves were previously normal.

Symptoms of Individual Organ Systems

Skin and Mucous Membranes. Pallor is almost invariably obvious. A characteristic appearance of the patient is often produced by a muddy pallor to which Libman has applied the descriptive term, "café au lait." Rarely, there is an erythema of the nose and adjacent parts of the cheeks resembling that of acute lupus erythematosus.

The most frequent skin lesions are *petechiae,* those with so-called white centers (actually yellowish-gray) being especially significant. The white centers are not raised in the subacute cases as they are in some of the acute bacterial cases. The petechiae are most frequently and best observed in the conjunctiva, especially of the lower lid,[126] in the fundus, in the skin about the clavicles,

and in the oral mucosa, particularly on the soft and hard palates. In ambulant patients, petechiae may also be found in the lower extremities. A characteristic feature is the occurrence of the petechiae in crops which disappear after several days and recur at a later period. However, isolated petechiae are also common.

Even more specific are tender cutaneous lesions, termed *Osler nodes.*[131] These are small, raised, swollen areas about the size of a pea, but they may be larger, or as small as a pinhead. Characteristically, they have a bluish tint but they may be pink or red, and rarely possess a blanched center. Most commonly they occur in the pads of the fingers or toes, in the thenar or hypothenar eminences, or the soles of the feet, and rarely on the sides of the fingers or on the webs between the toes. The essential feature of these lesions is that they are always tender. The patient may note their sudden onset because of the pain produced. In fact, painful fingers due to Osler nodes may be one of the chief complaints. The Osler node usually lasts one to several days but may disappear in a few hours. According to Libman[98] it is practically pathognomonic of subacute bacterial endocarditis.

The Osler node must be distinguished from the *Janeway lesion,*[79] which is more characteristic of acute bacterial endocarditis but is occasionally seen in subacute bacterial endocarditis. This is a small erythematous or hemorrhagic lesion which is sometimes raised and nodular but never painful. In subacute bacterial endocarditis it is more apt to appear as an erythematous lesion without a hemorrhagic or purple center. It usually occurs in the palms of the hands or the soles of the feet.

A rather characteristic lesion of the fingers, which may be embolic or toxic, is the so-called "splinter hemorrhage."[11] These are vertical hemorrhagic streaks in the skin under the nails.

Occasionally there are large, extensive purpuric lesions which may or may not be associated with thrombocytopenia, prolonged bleeding time and other typical blood findings of purpura hemorrhagica.

Kidneys. Hematuria, usually microscopic but occasionally gross, is commonly observed at some stage of the disease. As microscopic hematuria is very significant for diagnosis in a doubtful case, and as only a few red blood cells may be present in casual specimens, careful and repeated examinations should be made on centrifuged specimens of urine. Albuminuria is almost invariable, even when no glomerular lesions or infarcts are found.

Renal insufficiency occurs frequently. I have observed it in about 40 per cent of fatal cases. The percentage would probably have been higher had complete renal function studies been made. However, only about 15 per cent of the cases of subacute bacterial endocarditis in the active stage develop clinical symptoms of uremia. Usually renal insufficiency is denoted by a slight or moderate azotemia (urea nitrogen 25 to 75 mg. /100 cc.) and a fixation of urinary specific gravity to 1.010 by the concentration test. Even in the presence of renal insufficiency the blood pressure remains low. Renal insufficiency may be due to extensive glomerular embolization or to subacute diffuse glomerulonephritis. When the uremia develops, the usual symptoms of that condition are present and they are not infrequently the cause of death. But in the absence of uremia, renal insufficiency is denoted only by the changes in the urine and blood. A nephrotic syndrome occurs rarely.

Gross infarctions may be associated with pain as well as with hematuria and albuminuria. The pain may be located in the loin. It may radiate anteriorly

and into the groin as a result of the passage of blood clots along the ureter. Tenesmus and frequency of urination also occur.

Spleen. A large spleen is clinically palpable in about two thirds of patients. But even a large spleen may not be palpable either because the enlargement is very moderate or because the spleen is fixed to the diaphragm by adhesions. Splenic infarction may be characterized by sharp sudden pain in the left hypochondrium or the left lower axilla which may radiate to the left shoulder or precordium. There may be local tenderness and rigidity over the splenic region, and occasionally a rub is heard so that a pleurisy is diagnosed. In rare cases the infarcted spleen may rupture and lead to peritonitis, or peritoneal hemorrhage and sudden death. Sudden death may also result from rupture of a bacterial aneurysm of the splenic artery.

Heart. The presence of old cardiac murmurs and the development of new ones due to the bacterial infection have been mentioned. However, there may be no cardiac murmurs throughout the course of the disease.

Cardiac failure is relatively rare at the time bacterial endocarditis begins, i. e., subacute bacterial endocarditis usually attacks the well compensated cardiac patient. On the other hand congestive heart failure occurs commonly after the development of the bacterial infection. The association of active rheumatic carditis in about 25 per cent of the cases of subacute bacterial endocarditis accounts for some of the instances of heart failure. The sudden development of pronounced valvular insufficiency or the rapid increase in the bacterial destruction of previous valvular deformity is often responsible for the appearance of heart failure. While the anatomic changes in the heart muscle cannot be correlated with the presence or absence of failure, the toxic myocardial disturbances may exceed visible pathologic alterations. Cardiac failure has become the most important complication of bacterial endocarditis since the advent of antibacterial treatment with penicillin. For heart failure is often responsible for death even when the bacterial infection is eradicated.[179, 81] The heart failure may develop while penicillin is being administered or some days or weeks after satisfactory treatment has been concluded and bacterial vegetations sterilized.[47]

Disturbances of conduction are uncommon in contrast with their frequency in rheumatic fever.[146, 160] Patients with established auricular fibrillation are not apt to develop the disease.[100] However, exceptions do occur. In the cases of prolonged duration which have become bacteria-free, and in those in which congestive heart failure develops, auricular fibrillation is as common as in uncomplicated chronic rheumatic valvular disease. The most frequent disturbance in rhythm is a prolongation of the auriculoventricular conduction (P-R interval 0.21 to 0.36 second), which occurs in about 15 per cent of the cases. It is possible that in most of such cases there is a simultaneous active rheumatic infection but the bacterial vegetations may extend to involve the conduction system. Rarely there is widening and notching of the QRS complex. Complete heart block and bundle branch block may be due to the pressure of a bacterial aneurysm of the sinus of Valsalva on the interventricular septum. In one such case which I observed at autopsy there was partial heart block ending fatally with Adams-Stokes syndrome due to complete heart block.

A *pericardial rub* is rarely heard in subacute bacterial endocarditis, but it may be present if there is active rheumatic infection, uremia, or rupture or extension of a mycotic aneurysm into the pericardium.

Coronary occlusion may occur as a result of bacterial emboli from endocardial vegetations. In two such cases which I observed recently the lesion was found post mortem, but there were no obvious clinical manifestations. Such emboli may be responsible for sudden death or rarely for myocardial infarction.

Central Nervous System. Cerebral symptoms are a prominent feature of the disease.[91, 173] They may occur at the onset, or at any subsequent stage of the disease. The symptoms may resemble those of meningitis or encephalitis.[121] Meningitis is more common in the acute (especially pneumococcal endocarditis) than in the subacute cases. Paralyses are common. Usually the symptoms result from embolic occlusion of a large cerebral vessel. Rupture of an embolic aneurysm not infrequently causes a subarachnoid hemorrhage or fatal hemorrhage into the brain substance or intraventricular spaces.

Evidences of meningeal irritation are frequent and include, in addition to headache, dizziness and vomiting, stiff neck, exaggerated or absent deep reflexes and positive Kernig and Brudzinski reactions. The spinal fluid may vary considerably. Occasionally it is normal despite meningeal signs. Usually there is a bacterial or serous meningitis. In the latter there is an increased amount of protein in the spinal fluid, and polymorphonuclear cells but no bacteria. Not infrequently the fluid is bloody or xanthochromic due to a subarachnoid hemorrhage.

Encephalopathies may dominate the clinical picture. Usually they are associated with evidences of a meningeal reaction. There may be delirium, somnolence or stupor. When there are blurred vision, vertigo, diplopia, salivation, ocular paralyses, masked facies and muscular twitchings, the picture resembles an encephalitis. Paralyses of the upper motor neurone type are not uncommon. Clinically they appear as a crossed hemiplegia or a monoplegia with or without aphasia. They are caused by a bacterial embolus to a branch of the middle cerebral artery. Flaccid paralyses occur rarely, perhaps as a result of a funicular myelitis. The clinical picture may resemble that of poliomyelitis.

Respiratory Tract. Cough, dyspnea, nocturnal dyspnea and orthopnea are common pulmonary symptoms due to left heart failure. The cough may be quite irritating, and may also be due to enlarged tracheobronchial lymph nodes as suggested by Libman.[97]

Cough, chest pain, dyspnea and bloody expectoration may be due to pulmonary embolism. This is especially common in cases of bacterial endocarditis with vegetations on the tricuspid valve,[83] in right-sided bacterial endocarditis associated with interventricular septal defect and in bacterial pulmonary endarteritis complicating patent ductus arteriosus.[134] Pulmonary emboli may also be secondary to venous thrombi in the lower extremities. Occasionally cough and expectoration result from a complicating bronchopneumonia.

Liver. The liver is generally enlarged as a result of chronic passive congestion. Jaundice occurs occasionally and may be due to liver damage caused by prolonged cardiac failure or infection. It has been attributed to associated pulmonary infarction. Jaundice is said to occur with more than casual frequency in cases of gonococcal endocarditis. I observed it once in a woman of fifty-six with a subacute gonococcal endocarditis and concomitant with thrombocytopenic purpura. In this instance it was explained as being due to a large splenic infarct occurring in a patient with severe anemia, anoxemia and degenerative hepatic alterations.

Gastrointestinal Tract. Anorexia, abdominal pain, nausea and vomiting are not uncommon. The latter occurs particularly toward the end and may be due to toxemia, cardiac failure or a cerebral complication. Diarrhea occurs occasionally.

Extremities. Clubbing of the fingers is eventually present in about two thirds of the fatal cases in my experience. Cotton[27] first called attention to this symptom, having found that of 63 cardiac patients with this abnormality 44 had definite evidence of bacterial endocarditis. Blumer[11] noted clubbed fingers in 18 of 48 cases. Clubbing of the toes is also frequent.

Occasionally the patient with subacute bacterial endocarditis suffers an acute episode in which the ends of the extremities suddenly become cold and cyanotic or mottled with purplish red blotches. The fingers and toes (also the tip of the nose) develop areas of bluish necrosis. These manifestations usually indicate a ball-valve thrombus occluding the mitral orifice.[154]

Joint pains are not uncommon or there may be less localized pain in the extremities. Pain in the fingers, due to Osler nodes or a subungual hemorrhage, has been mentioned. There may be a true polyarthritis due to coincident active rheumatic infection. Arthralgias are especially common in the cases of endocarditis due to brucella or meningococcus and arthritis is common in subacute gonococcal endocarditis.

Sudden pain, loss of function, coldness, pallor or cyanosis results from embolization of a large vessel to an extremity. Gangrene may follow.

Eyes. White-centered petechiae in the conjunctiva are frequent and important for diagnosis. They may occur singly or in crops lasting several days. Petechiae with and without white centers are also encountered in the retina.[69] Often these petechiae have a characteristic boat-shaped appearance.[43] White-centered retinal hemorrhages may also be observed in cases of leukemia, severe anemia, scurvy and various bacteremias. Whitish lesions known as Roth spots are observed both in acute and subacute bacterial endocarditis as well as in other diseases with severe anemia.[145]

Optic neuritis and even choked disk have been described as toxic manifestations of the disease.[46, 38] Usually vision appears unimpaired. Recently Kauntze[84] reported 7 cases of subacute bacterial endocarditis in which optic neuritis occurred at the onset or as an early manifestation. The neuritis is attributed to vascular occlusion and impairment of blood supply to the nerve. The cases with papilledema which I have observed have been associated with meningeal symptoms, a serous meningitis or subarachnoid hemorrhage. The finding of optic neuritis in association with other neurologic abnormalities is often responsible for diagnostic error.

Sudden blindness may result from embolism of the central retinal artery. I have also seen a patient in whom fever and a quadrant defect in the visual field (due to embolism of a retinal arterial branch) were the only manifestations of subacute bacterial endocarditis.

The *pathologic changes* in the retina and choroid have been described by Dienst and Gartner.[42] They include papillitis, edema and cellular infiltrations surrounding the retinal blood vessels and the optic nerve. The choroid is especially involved with dense foci of cellular infiltrations, chiefly small round cells.

Vessels. Embolization and arteritis are important manifestations. Gross embolization with infarctions generally involves the extremities, the spleen, the

kidneys, the lungs and the brain. The symptoms have been described in connection with the organs affected. Smaller emboli or toxic inflammation of vessels probably account for the various cutaneous and fundal lesions and the microscopic hematuria of embolic glomerulonephritis. Phlebitis and tender swellings of the walls of arteries have been described.

Blood. A *positive blood culture* of the Streptococcus viridans or other causative organisms is obtained in the majority of cases. This is discussed under etiology and diagnosis.

Anemia is a feature of the disease. Usually the hemoglobin averages between 50 and 70 per cent (8.5 to 12 gm. per 100 cc.). The hemoglobin drops progressively during the disease. In about 10 per cent of cases the anemia is intense, the hemoglobin falling below 7 gm. and the erythrocytes below 2.5 million. In patients with purpura I have seen the hemoglobin as low as 3.4 gm. The red blood count is usually between 2.5 and 4 million. When the infection is controlled by antibiotics there is a rapid increase in hemoglobin and erythrocyte levels.

Leukocytosis is, in my experience, not characteristic unless there is some complication. More than one third of the patients I have studied have had a white count under 10,000. Seabury[158] encountered leukocyte counts between 5000 and 10,000 in 53.4 per cent of his cases. It is important to emphasize this because many physicians tend to exclude subacute bacterial endocarditis as a diagnostic possibility when the white blood count is not elevated. Thayer's[170] series shows that counts above and below 15,000 are equally frequent. I have observed that the highest count (20,000 to 40,000) occurred with meningeal and cerebral complications. White counts between 15,000 and 25,000 were generally associated with embolism, active rheumatic infection or a concomitant pulmonary infarction. When a leukocytosis was present, independent of these conditions, it was of mild degree (10,000 to 14,000), and the polymorphonuclear leukocytes were between 65 and 88 per cent with a "shift to the left" in the Schilling hemogram. Occasionally there is a leukopenia. I once saw a white count of 2,400 in a patient with subacute bacterial endocarditis complicated by lobar pneumonia.

There may be a pronounced monocytosis.[155] Sometimes the blood contains large phagocytic cells varying in size between 10 and 80 micra.[149] These macrophages, histiocytes or endothelial cells, as they have been variously termed, may dominate the blood picture and are helpful in confirming the diagnosis.[149] I do not believe, however, that they are pathognomonic or that they are frequently observed.

The *blood platelets* are usually normal. Not infrequently they are reduced in number and rarely to such low levels that they may produce purpuric manifestations.

There is often an elevation of the blood proteins due entirely to an *increase in the serum globulin fraction*. The latter accounts for the frequently positive formol-gel reaction and for frequently positive cephalin-cholesterol flocculation and thymol turbidity tests in subacute bacterial endocarditis. This disease is associated with increased activity of the reticuloendothelial system which is important in the formation of antibody globulin.

The *sedimentation rate* of erythrocytes is distinctly accelerated in subacute bacterial endocarditis. Increased serum globulin and fibrinogen as well as anemia account for this finding.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The complete diagnosis of subacute bacterial endocarditis is based on the presence of (1) a valvular defect or congenital cardiovascular lesion, denoted by a murmur, (2) a febrile course, (3) embolic phenomena, (4) a positive blood culture. However, the urgency of early diagnosis and early institution of specific therapy demands an alteration in our criteria for diagnosis. Therapeutic failure may result from delay until the full clinical picture is unfolded or rigid diagnostic criteria are satisfied. Blood cultures may remain persistently negative in 10 to 25 per cent of active cases of subacute bacterial endocarditis, even with excellent technic.[100, 106] In other cases a positive culture is obtained only after repeated attempts. Furthermore embolic phenomena often appear relatively late in the course of the disease.

The diagnosis of subacute bacterial endocarditis should be assumed as most probable whenever a patient with an organic cardiac murmur experiences fever, without apparent cause, for more than one week. Often, at this stage, a meticulous search will provide strong diagnostic confirmation in the finding of white-centered petechiae in the conjunctiva, fundus or palate or Osler nodes. A positive blood culture is desirable for definite diagnosis, and as a guide to the choice of antibiotic and dosage in treatment of the disease. However, treatment need not await isolation of the causative organism if the diagnosis is reasonably probable on clinical grounds (p. 785). Splenomegaly, anemia, clubbed fingers or microscopic or gross hematuria adds diagnostic support but if ideal early treatment is to be administered, the diagnosis should be made in most cases before any of these abnormalities appear. Most common febrile diseases due to infections of the upper respiratory tract or other cause clearly reveal their nature or subside within a week. If the fever persists and its origin is still obscure at the end of that period in a patient with a cardiac murmur, a blood culture, agglutination tests and other laboratory or roentgenologic studies should be made to confirm the tentative diagnosis of subacute bacterial endocarditis or to discover some other cause of the fever. A therapeutic test with salicylates, carefully interpreted, may be of help in distinguishing active rheumatic infection. But it should be recalled that subacute bacterial endocarditis and rheumatic activation often coexist.

In the absence of a cardiac murmur, the diagnosis may be extremely difficult but this difficulty is rarely encountered except in the acute bacterial cases. In the absence of a murmur, the diagnosis depends on the taking of blood cultures in all cases of unexplained fever and on the search for white-centered petechiae, Osler nodes, hematuria, splenomegaly, clubbed fingers or embolic phenomena. The development of an organic cardiac murmur, not present previously, is often the clue to diagnosis, but unfortunately a late one. In doubtful cases of prolonged unexplained fever without a cardiac murmur it may be preferable to give the patient a therapeutic trial with penicillin as if he had bacterial endocarditis than to await serious and irreversible evidences of the disease.

Blood Cultures. Blood cultures, formerly important only in diagnosis, have acquired additional importance because proper treatment is most likely when the causative organism is identified and its sensitivity to individual antibiotics is determined. With proper technic positive blood cultures are usually obtained in 75 to 90 per cent of cases. Occasionally mixed infections occur and care must be taken to isolate and identify both of the causative microorganisms.

Successful blood cultures require the use of aseptic technic, adequate amounts of blood (preferably 20 to 25 cc.), a variety of fluid and solid media, some of which are enriched with dextrose, tomato, liver, hormones, ascitic fluid, etc., anaerobic as well as aerobic conditions of growth, prompt incubation and prolonged observation. As a rule a positive culture will reveal growth within one to four days, but occasionally I have observed growth only after two or three weeks. The gonococcus often grows with difficulty and the Hemophilus influenzae group not infrequently requires long periods for visible growth. In suspected cases of subacute bacterial endocarditis with negative cultures it may be necessary to employ special media for the possible isolation of higher bacteria, spirilla or fungi.

Negative blood cultures in definite cases of subacute bacterial endocarditis[85] may be due either to improper technic or to absence or paucity of microorganisms in the blood at the moment of collecting the sample. A positive blood culture requires the escape of a large number of bacteria into the blood from the focus on the valvular or mural endocardium. Sometimes a positive culture of Streptococcus viridans may be obtained in the absence of bacterial endocarditis, e.g., in about 6 per cent of cases of rheumatic fever and other unrelated diseases according to Lichtman and Gross.[103] Such transient bacterial invasions of the blood stream in normal individuals have also been noted following the extraction of teeth or tonsils. Usually, however, in such cases the streptococci grow only in fluid media while in subacute bacterial endocarditis they also appear in numerous colonies on the solid media.

Differential Diagnosis. Subacute bacterial endocarditis must be distinguished from a host of diseases responsible for more or less prolonged fever and from numerous systemic diseases which are simulated by embolization of various organs. Anorexia, weight loss, anemia and low grade fever may suggest the presence of a malignancy. Not infrequently the combination of pronounced splenomegaly, anemia and fever leads to a diagnosis of abdominal Hodgkin's disease, cirrhosis of the liver, Banti's syndrome (congestive splenomegaly), or some hematologic disturbance.

The most common errors are the diagnoses of "grippe," "virus infection" or influenza early in the course of the fever, and active rheumatic infection when the fever persists. A search for white-centered petechiae, Osler nodes, splenomegaly and microscopic hematuria, and cultures of the blood will usually distinguish subacute bacterial endocarditis from the above. Sometimes *Libman-Sacks disease* (acute disseminated lupus erythematosus) resembles subacute bacterial endocarditis in the presence of prolonged fever, albuminuria and hematuria and occasionally an Osler node or white-centered petechia. But almost invariably the patient with Libman-Sacks disease is a female, an organic cardiac murmur is exceptional, moderate leukopenia is usual, blood cultures are negative and there is a distinctive butterfly skin lesion over the bridge of the nose and cheeks. So-called L. E. cells may be found in concentrated marrow.[72a]

When the clinical picture is dominated by embolic involvement of a given organ, the following diagnostic errors are common: (1) the diagnosis of a cerebral thrombosis or hemorrhage or meningitis when the onset or dominant symptoms are due to cerebral embolism or rupture of a cerebral mycotic aneurysm; (2) the diagnosis of chronic pyelonephritis, chronic renal tuberculosis, glomerulonephritis, or renal calculus disease with urinary infection when the onset or dominant manifestations of subacute bacterial endocarditis are

due to renal vascular emboli or glomerular vascular lesions. In all such cases the finding of a cardiac murmur should put the examiner on guard as to the possibility of a bacterial endocarditis. Blood cultures and the search for other clinical manifestations will usually confirm this tentative diagnosis.

Diagnosis of the probable causative organism in subacute bacterial endocarditis may sometimes be inferred from the clinical history and findings. This may be helpful in determining the use of most favorable media and technics for blood culture.

Enterococcus endocarditis has been described as a distinct clinical entity[140, 63] but in my experience neither the clinical picture nor the postmortem findings differ significantly from those of subacute bacterial endocarditis due to Streptococcus viridans. Valvular heart disease, fever and toxemia, splenomegaly, white-centered petechiae, Osler nodes, embolic phenomena and nephritic symptoms are usually present. On two occasions, infarcts which I observed post mortem were soft and purulent. The causative organism often enters the blood stream from infections of the urinary tract. In several cases which I observed enterococcus endocarditis followed an abortion with subsequent pelvic peritonitis and phlebitis.

Gonococcal endocarditis[190, 32] may be suspected from certain special features. Often there is a history of recent gonorrhea two to four weeks earlier, or an abnormal vaginal discharge is still present. Arthritis is usually present at the time of observation or has recently subsided. Often endocarditis is overlooked, the fever being attributed to the arthritis. Chills and high fever are much more common than in the usual subacute streptococcal endocarditis. A daily double-peaked rise in the temperature curve (double quotidian type of fever) has been described as characteristic of gonococcal endocarditis[56] but it has also been observed in endocarditis due to the meningococcus.[48] Skin lesions, besides petechiae and Osler nodes, occur commonly in gonococcal endocarditis and may be characteristic.[52] They consist of crops of macules or papules, which are often hemorrhagic, on the extremities and trunk and occasionally on the neck. The crops usually persist two to five days. There may be isolated vesicular or pustular lesions without organisms. A chronic glomerulonephritis is very common. Jaundice is said to occur more often than in subacute bacterial endocarditis due to other organisms. A cardiac murmur may be due to preexisting valvular or congenital heart disease or it may develop as a result of the bacterial deformation of a valve. The pulmonic valve is more likely to be affected than by other organisms.[124]

Meningococcus endocarditis[125, 48] may be suspected when to the combination of an organic cardiac murmur and fever there are added arthralgias, crops of macules, papules or urticarial-like skin lesions, but no history of gonorrhea or arthritis. Firestone[48] described a typical fever curve of the "double quotidian type" as in gonococcal endocarditis. A chronic meningococcemia may occur without endocarditis.

Brucella endocarditis[168] may be suspected when an organic cardiac murmur, unexplained fever and arthralgias occur in an individual who works in a slaughterhouse or meat packing house, or who drinks unpasteurized milk or who has intimate contact with cattle or pigs infected with brucellosis. Blood cultures should be made in an atmosphere containing 10 per cent CO_2 as well as aerobically, and blood cultures should not be discarded for four to eight weeks, as growth may be very slow.

Endocarditis due to the Streptobacillus moniliformis or to the Spirillum minus may be suspected when the clinical picture of subacute bacterial endocarditis with multiple arthritis and macular or papular erythema occurs in an individual with an history of rat-bite or of intimate contact with rats. In the cases due to Spirillum minus, the incubation period is longer (more than ten days). The local bite lesion is likely to flare up with the development of endocarditis. Arthritis is usually absent, and the skin lesions are larger and papular while in the cases due to the streptobacillus the skin lesions are morbilliform and petechial. But the clinical picture may be similar in both and both respond to penicillin therapy. The causative organisms may be better grown in an atmosphere containing CO_2 than aerobically.

Erysipelothrix endocarditis. A history of handling fish, game or cheese or of polishing fish bones in button making, and the presence of an erysipeloid skin lesion together with the clinical picture of bacterial endocarditis, suggest that the latter is due to the erysipelothrix.

Subacute bacterial endocarditis in older age groups is often overlooked.[5, 192] The not infrequent occurrence of rheumatic cardiovalvular disease after the age of sixty[54, 57] suggests the likelihood that bacterial endocarditis also may develop beyond that age. Difficulties in diagnosis arise because multiple diseases in elderly people mask the endocarditis, or because of the tendency to explain the clinical findings by an occult neoplasm, prostatism and urinary tract infections, or by arteriosclerotic, coronary or cerebral vascular disease. Congestive heart failure and renal insufficiency are especially frequent in cases of subacute bacterial endocarditis in the aged. Bacterial embolic cerebral manifestations in the elderly are usually interpreted as due to cerebral thrombosis or hemorrhage. Despite these difficulties, the diagnosis will not be overlooked if the possibility of bacterial endocarditis is considered whenever there is a cardiac murmur and fever and if thereupon blood cultures are made, as well as careful, repeated observation for white-centered petechiae, Osler nodes and splenomegaly.

THE BACTERIA-FREE STAGE. TRANSITIONAL HEALING CASES

Libman[98] described a number of cases of subacute bacterial endocarditis which were in the "bacteria-free stage." Postmortem examination revealed healed bacterial vegetations in which bacteria were absent or dead and calcified. The appearance of the vegetations in these spontaneously healed cases was essentially like that of vegetations which have been sterilized and healed with the aid of penicillin.[118] In the spontaneously healed (bacteria-free) cases, diffuse glomerulonephritis and fibrosis and hyalinization of the focal glomerular lesions are common. The spleen is usually more enlarged than in the active stage.

Clinically, there may be a history of a valvular defect and a cardiac murmur is discovered on examination. Symptoms and signs of congestive heart failure, renal insufficiency with azotemia, and unexplained severe anemia with pronounced splenomegaly are the cardinal features. There may be a striking dark brown pigmentation of the face.

Blood cultures are negative because there are no bacteria in the vegetations to enter the blood stream. However, negative blood cultures, per se, do not denote the bacteria-free stage in a suspected case of bacterial endocarditis. For even when the disease is active and live bacteria are embedded in the vegeta-

tions, blood cultures may be negative either because none or too few bacteria have entered the blood stream at the time the culture is made or because blood culture technic is imperfect.

The diagnosis of the bacteria-free stage should be entertained in an afebrile patient with valvular or congenital heart disease, who has an unexplained severe anemia and splenomegaly, and/or renal insufficiency with azotemia. The renal insufficiency is associated with low or normal blood pressure.

Of more frequent occurrence, in my experience, are *transitional healing cases* in which bacteria are still present in small numbers in the vegetations, insufficient to give a positive culture but capable of causing fever and toxemia. The clinical picture is essentially like that of the bacteria-free stage, but fever, moderate toxemia, occasional petechiae and sterile emboli are added to the anemia, splenomegaly, renal insufficiency and heart failure.

Recovered cases, due to early adequate penicillin therapy, should be distinguished from the spontaneous bacteria-free stage because there need be neither heart failure, renal insufficiency, anemia nor splenomegaly. Only the original valvular defect and subsequent bacterial damage remain. However, when treatment is delayed or the bacterial damage to valves, myocardium or kidneys is too extensive by the time sterilization is accomplished with antibiotics, persistent cardiac failure or renal insufficency may develop as in the spontaneously bacteria-free cases.

TREATMENT

Penicillin is therapeutically effective in the great majority of cases of subacute bacterial endocarditis. Occasionally streptomycin is curative when penicillin is not. When neither penicillin nor streptomycin can control the infection, it may be advisable to resort to the sulfonamides as the latter appeared to achieve occasional cures in the pre-penicillin era. The sulfonamides may then be employed alone or in combination with an antibiotic. Dihydrostreptomycin has now replaced streptomycin, and aureomycin and chloromycetin are promising newer antibiotics which may be given orally (infra).

Principles of Antibiotic Treatment

The following principles should guide the use of antibiotics in treating subacute bacterial endocarditis:

(1) Treatment should begin as early as possible before fatal or irremediable complications occur.

(2) Adequate dosage should be administered, i.e., amounts which are suitable in each case to destroy the responsible organism found by blood culture. The effective dosage is determined and modified by sensitivity tests, repeated blood cultures and observation of the clinical course.

(3) Antibiotic treatment should be continued long enough to sterilize completely all bacterial vegetations and all possible embolic foci.

Commencement of Treatment

Early treatment demands early diagnosis (p. 793). But delay in treatment may be due not only to faulty diagnosis but also to a desire to confirm the diagnosis by blood culture and to determine the sensitivity of the causative organism. Sometimes blood cultures are repeatedly negative in clinically definite cases of subacute bacterial endocarditis. In such cases particularly, the

delay in instituting treatment is likely to be protracted. I have been so impressed by the importance of early treatment in order to avoid irreversible complications that I commence penicillin therapy whenever the diagnosis of subacute bacterial endocarditis appears probable on clinical grounds.

Blood cultures are then made on two successive days and therapy is begun immediately after blood is drawn for the second culture. One million units of penicillin are given daily until reports of the blood culture are obtained. If the blood culture is positive, the sensitivity of the organism to penicillin is determined and the dosage is increased or diminished accordingly, or streptomycin is substituted if the organism is sensitive to the latter but not to penicillin. If the blood cultures are negative, the clinical diagnosis should be reviewed. If subacute bacterial endocarditis still appears probable, the dosage is continued if there is a favorable therapeutic response or increased if the response is unsatisfactory. Blood cultures should be repeated at weekly intervals or when there is a sharp rise in temperature.

Sensitivity of the Causative Organism

The sensitivity of the causative organism is determined in vitro by some modification of the Oxford cup test or by serial dilution in test tubes.[50, 34] The following is a résumé of a satisfactory procedure:

(1) A stock solution of penicillin containing 250 units per cc. of saline is kept in the refrigerator. The required dilutions are made with plain broth or with other suitable media for the bacterium to be tested. Dilutions are made over the likely range of sensitivity of the organism as indicated by previous experience, e.g., from 0.01 unit of penicillin per cc. of broth to 1.0 unit per cc.

(2) Bacterial suspensions of the organism to be tested are made up from six hour cultures, or in the case of meningococci and gonococci from twenty-four hour cultures. For uniformity, the concentration of staphylococci should be about 600 bacteria per cc., for streptococci and pneumococci 3 to 4 million per cc. and for anaerobic bacteria 5000 to 50,000 per cc.

(3) One cubic centimeter of bacterial suspension is mixed with the penicillin media dilutions in a series of tubes containing respectively 0.8, 0.7, 0.6, etc. unit of penicillin per cc. The total volume in each tube is 2 cc. After twenty-four hours' incubation, one notes the lowest concentration of penicillin which completely inhibits the growth of the organism, as indicated by the absence of turbidity. This represents the sensitivity of the organism. If the concentration of penicillin in this tube is multiplied by 25, the sensitivity is expressed in Oxford units.

(4) For control, a similar test series is set up, using a standard test organism, usually a Staphylococcus aureus or Streptococcus hemolyticus. In each test series one of the test tubes should contain no penicillin and growth must appear in this tube if the determination is valid.

The standard organism employed by many observers is inhibited by an average of 0.02 Oxford units per cc. of the growth mixture. By comparison the penicillin sensitivity of the Streptococcus viridans and other nonhemolytic streptococci responsible for subacute bacterial endocarditis usually ranges from 0.007 to 0.5,[105] (Loewe); 0.02 to 0.05[63] (Goerner et al.); 0.015 to 0.08[117] (Mokotoff et al.); 0.008 to 0.14[35] (Dawson and Hunter), and 0.008 to 0.03[114] (Meads et al.). As a rule the resistance of these organisms to penicillin varies between one and four times the resistance of the standard organisms, but I

have observed nonhemolytic streptococci in cases of subacute bacterial endocarditis (usually enterococci) which were 50 to 250 times as resistant as the standard staphylococcus, i.e., 1 to 5 units of penicillin per cc. were required to inhibit growth.

Determination of Serum Level of Penicillin. By a similar procedure the penicillin level in the blood can be determined after therapy is begun. Of a series of tubes containing 0.8, 0.7, 0.6 cc. of serum, etc., each is made up to 1 cc. with broth and mixed with a 1 cc. suspension of a young culture of the test organism. The 2 cc. mixtures are incubated for twenty-four hours and the lowest concentration of serum required to inhibit the growth of the standard organism is observed. Since the sensitivity of the standard organism is known in terms of Oxford units, it is possible to calculate the number of Oxford units of penicillin per cc. of serum. Or else the same procedure is repeated using known concentrations of penicillin in broth in place of the body fluid. If the amount of serum and the known concentration of penicillin necessary to inhibit the same bacterium in the same test volume are equated, the concentration of penicillin in serum can be calculated. Experience and knowledge of the dose of penicillin administered facilitate the arrangement, in advance, of the proper range of serum dilutions to be used in the test.

Dosage of Penicillin. Early experiences with penicillin therapy in subacute bacterial endocarditis disclosed that larger doses and longer treatment were required than in most of the common infections due to other gram-positive organisms or to gram-negative cocci. Loewe[105] achieved control of the infection in more than half of his early cases with 200,000 units of penicillin daily for two weeks. An enlarged experience has taught the need for higher dosage and more prolonged administration of penicillin if optimal results are to be attained.

It is probable that 500,000 to 800,000 units of penicillin daily can control the bacterial infection in about 90 per cent of the cases of subacute bacterial endocarditis due to the usual causative organisms. If the diagnosis is reasonably certain and treatment is begun before a positive blood culture can be obtained, it is preferable to start with at least 1,000,000 units daily. When the causative organism has been grown from the blood stream, its in vitro sensitivity to penicillin should be determined and dosage adjusted accordingly. While in vitro sensitivity is not an absolute guide to proper dosage, it is the most satisfactory one available until the clinical response can be observed. Experience has taught that the best clinical results are obtained when penicillin is administered in dosages sufficient to maintain a serum concentration of five to ten times that which inhibited the growth of the organism in the test tube.

As a tentative guide the following schedule has proven useful when the sensitivity of the organism is known:

500,000 units daily if it is sensitive to less than 0.04 units per cc.
800,000 units daily if it is sensitive to 0.05 to 0.1 units per cc.
1,000,000 units daily if it is sensitive to 0.1 to 0.2 units per cc.
1,600,000 units daily if it is sensitive to 0.2 to 0.3 units per cc.
2,000,000 units daily if it is sensitive to 0.3 to 0.4 units per cc.
5,000,000 units daily if it is sensitive to 0.4 to 0.9 units per cc.
6,000,000 to 10,000,000 or higher units daily for bacteria requiring 1 unit or more of penicillin per cc. in vitro.

For more resistant organisms, dosage must be individualized with particular

care in order to be certain that sufficiently high blood levels of penicillin are attained to sterilize the blood stream. When more than 2 million units must be given daily it may be advantageous to enhance the penicillin blood levels by giving caronamide (p. 802) simultaneously. I have observed several patients in whom bacterial endocarditis was caused by microorganisms 50 to 150 times as resistant as the standard organism, i.e., their growth was inhibited by 1 to 3 units per cc. of penicillin. Cure was effected by penicillin in doses varying from 5 to 10 million units daily intravenously for the organisms of lower resistance, to 10 to 15 million units daily for the more resistant organisms. In a case caused by a still more resistant organism (Veillonella gazogenes, requiring 10 to 15 units per cc.), an effective result followed the use of 10 million units of penicillin daily, supplemented by 240 gm. daily of sodium para-aminohippurate for sixteen days.[109]

After the trial dosage has been given, it is desirable to determine the blood level of penicillin in order to check whether the required concentrations have been achieved. If not, dosage should be increased as indicated. Most important, the dose should be modified according to the clinical response. Negative blood cultures within a day after beginning treatment, a fall in temperature, disappearance of subjective symptoms and improved appetite, all within a week, denote a satisfactory effect and adequate dosage. Otherwise successive increases in dosage should be made weekly. Low grade fever and occasional petechiae or Osler nodes do not necessarily preclude a satisfactory course. But persistently positive blood cultures almost always indicate the need for higher penicillin dosage. Exceptionally, in cases of long delay before treatment, I have seen a cure effected without change of dosage, even though cultures remained positive for one month after treatment was begun. Of course the penicillin blood levels were adequate according to the in vitro determinations.

Bacterial endocarditis occurring in the course of pregnancy should be treated as above.[33]

Duration of Treatment

The optimum period of treatment has not yet been established and probably varies with the individual case. *Inadequate duration* of treatment is the common cause of recurrence in cases in which *adequate daily dosage* accomplished a temporary clinical "cure" and sterilization of the blood stream.

Empirically, *five weeks of continuous treatment with adequate daily dosage* appears to be the minimum desirable period, even though cures have been effected with briefer courses of penicillin therapy. But the duration of treatment should be extended beyond five weeks, in proportion to the delay in commencing treatment for more than a month after the onset of the disease. Treatment should also be prolonged if previous courses were unsuccessful, especially if dosage was apparently adequate, or if serious complications are present.

Methods of Administration of Penicillin

The preferred methods of administering penicillin to patients with bacterial endocarditis are by continuous intravenous infusion (venoclysis), by intermittent intramuscular injections at two- to three-hour intervals or by continuous intramuscular injection. But recent experiences indicate that for most cases due to organisms of usual sensitivity the intramuscular administration of

penicillin-procaine preparations at twelve to twenty-four hour intervals will supersede the above methods of therapy.

Continuous Intravenous Infusion. When given by continuous venoclysis the total dose for twenty-four hours is dissolved in not more than 1500 cc. of 5 per cent glucose in distilled water and the rate of infusion adjusted for this amount of fluid. Or aliquot proportions may be prepared for eight- or twelve-hour periods. Saline solutions should be avoided because of the frequent development of congestive heart failure.

The chief advantage of this method is the continuous maintenance of the desired level of penicillin. For high doses of penicillin (5 million or more units daily), this is the method of choice. The disadvantages are the need for sterilized apparatus not easily available for treatment at home, and the need for relatively close and continuous supervision to avoid or correct an interruption of flow. Thrombophlebitis at the site of infusion occurs not infrequently, and local perivenous infiltrations may make the veins inaccessible before treatment is completed.

Intermittent Intramuscular Injections. One eighth of the daily dose of penicillin, dissolved in 2 to 4 cc. of saline with 1 per cent procaine, is injected intramuscularly every three hours, day and night. Since the level of penicillin in the blood may reach a peak in twenty to thirty minutes and fall to traces or zero after two hours, there is a theoretical objection to the long intervals between intramuscular injections. For this reason the intramuscular injections have been given every two hours or even every hour day and night. However, experience has demonstrated equally satisfactory results with the three-hour intervals as with the more frequent injections or with continuous venoclysis. The greater practicability of the longer interval outweighs the theoretical objection. The therapeutic possibility of further prolonging the intervals between injection by giving the daily dose in a long-acting penicillin-procaine compound by one or two injections is being investigated. After a single dose of 600,000 units, an average penicillin level of 1.0 unit was found in the plasma. This denotes that two intramuscular injections daily, twelve hours apart, would suffice to control the vast majority of causative organisms, except those unusually resistant. Several cures have been effected with penicillin-procaine in this dosage, continued for five to eight weeks.[144, 53] It is highly probable that in the great majority of cases due to organisms of usual sensitivity, one or two daily injections of 600,000 units of procaine-penicillin over a period of five to eight weeks will suffice.

The chief advantage of intermittent intramuscular injection is the simplicity of preparation and administration of the penicillin solution. The chief disadvantage is the local pain and the psychic trauma associated with the repeated injections. However, local pain is minimal or absent when the procaine-penicillin preparations are used either in aqueous solution or in oil with 2 per cent aluminum monostearate.

Other Methods of Administration. Combined use of continuous intravenous infusion and intermittent intramuscular injections is frequently advisable when difficulties with the veins or pain and local reactions in the muscles require interruption of one or the other methods.

Continuous intramuscular infusions have been recommended[73, 93] but have proved less satisfactory than the above, chiefly because of local pain and edema.

Oral penicillin is impracticable at present because of uncertain absorption and the average requirement of five times the parenteral dose to achieve the same blood level.

Adjuvants to Penicillin Therapy

A variety of drugs enhance the blood level of injected penicillin by restraining the latter's excretion through the kidneys. Benzoic acid, diodrast and para-aminohippuric acid were first employed but more recently caronamide[7, 8, 30] has proved most advantageous. The caronamide may be given orally in 3 to 4 gm. doses, every four hours.[191a] By inhibiting renal tubular excretion of penicillin, blood levels of the latter may be increased to levels three to six times that attained by the same dose of penicillin alone.[107,159] The caronamide may thus be employed to conserve penicillin, to diminish the number of injections given daily or to attain extremely high blood levels in cases due to very resistant microorganisms.

Heparin or other anticoagulants have no place in the treatment of subacute bacterial endocarditis and may be dangerous.

Clinical Response to Penicillin

In favorable cases the patient's general condition improves and his appetite and sense of well being are restored within a day or two after treatment is begun. Blood cultures may become sterile within four hours and usually within twenty-four hours. Fever usually subsides by the end of a week; it may persist as long as penicillin is being administered, but at lower levels than before treatment. In the absence of continued active bacterial endocarditis or of bacterial embolization, persistent fever may also be due to thrombophlebitis at the sites of venoclysis, concomitant intercurrent upper respiratory, tonsillar or dental infection, or active rheumatic infection. A therapeutic test with salicylates is desirable. Petechiae and emboli usually cease after the first week of successful therapy but may recur for many weeks even in cases with favorable outcome. Despite these exceptions persistent fever, embolization and petechiae should stimulate a review of the adequacy of penicillin dosage. With a favorable response to penicillin, the hemoglobin rises, leukocytosis subsides and the sedimentation rate falls. But the latter may not return to normal for several weeks after treatment is discontinued.

Toxic effects of penicillin are relatively infrequent and mild. The commonest are itching, urticaria and angioneurotic edema, which develop during treatment or in the following few weeks. The urticarial symptoms are almost always readily controlled by the administration of pyribenzamine or benadryl. The penicillin should not be discontinued.

Other Antibiotics and Chemotherapy

A small percentage of nonhemolytic streptococci, notably some of the enterococci (Streptococcus fecalis), as well as the Hemophilus influenzae and other gram-negative bacilli which occasionally cause subacute bacterial endocarditis, are resistant to penicillin even in large doses. The antibiotic, *streptomycin,* has been found effective against these gram-negative bacilli (H. influenzae, Brucella melitensis and abortus, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa and E. coli). It may be more effective than

penicillin against some of the enterococci. Tests of the sensitivity of the causative organism to streptomycin should be performed, similar to those described with penicillin.

Dosage consists of 1 to 3 gm. daily, according to the sensitivity of the organism in vitro and the ability to attain adequate inhibiting levels of streptomycin in the blood stream. The methods of administration are similar to those for penicillin. Therapy should be continued for five weeks in the absence of serious toxic symptoms. Only isolated reports of successful treatment of subacute bacterial endocarditis with streptomycin have been made.[136, 167, 29, 120a]

The chief toxic symptoms are vertigo and hearing impairment due to damage to the eighth nerve. These are apt to occur with the higher dosage and with prolonged therapy. Another disadvantage is the frequent increase in resistance of the organism during the course of treatment.

Dihydrostreptomycin, an antibiotic produced by the hydrogenation of streptomycin, is similar to the latter in action and effectiveness and may be administered in identical dosage. It possesses the advantage of causing a much lower incidence of dizziness and disturbances in equilibrium and therefore should entirely replace streptomycin in the treatment of appropriate cases of bacterial endocarditis. Related experimental products promise additional advantages including relative freedom from the development of resistant strains.

Aureomycin and *chloromycetin* are newer antibiotics which should prove useful in the treatment of cases of bacterial endocarditis due to gram-negative rods, including some of those resistant to streptomycin. They possess the advantage of being effective orally and relatively nontoxic.

Sulfonamides should be given a therapeutic trial if the antibiotics are ineffective because of resistance of the organism.[153] They may be more effective when combined with penicillin, streptomycin or both.[113] Prior to the advent of penicillin there were indications that sulfonamides were responsible for a small increase in the number of recoveries. The most promising results seemed to follow the use of massive doses given intravenously as recommended by Dick,[40] e.g., 25 to 40 gm. in an initial single dose followed by subsequent oral dosage of 4 to 8 gm. daily for five or more weeks if tolerated.

Surgical Treatment

Ligation and section of a patent ductus arteriosus has cured patients with subacute bacterial endarteritis associated with this congenital defect.[175, 12] Surgical ligation cures not only the infection in the ductus and pulmonary artery but also the anatomic and the resulting physiologic and clinical disturbances. If the causative organism is sensitive, treatment should begin with antibiotics and surgical ligation should be performed at a later date to eliminate existing symptoms and to avoid subsequent reinfection or circulatory disturbances. If the causative organism is too resistant, surgical ligation and section of the patent ductus should be done at once. (See also p. 663.)

Resection of an infected arteriovenous aneurysm has cured cases of subacute bacterial endarteritis engrafted on the aneurysm.[70, 174, 104, 161, 168a] Delayed treatment may mean secondary infection of the heart valves with bacterial endocarditis as well as endarteritis. As with an infected patent ductus, antibiotic therapy should be instituted if the organism is sensitive. Later, excision of the aneurysm is indicated to avoid reinfection and circulatory insufficiency.

Mycotic emboli and aneurysm occasionally require surgical removal or excision while the general infection is controlled by antibiotic therapy. The successful excision of a mycotic aneurysm of the brachial artery following cure of a bacterial endocarditis was reported by Hurwitz and Arst.[77]

Prophylactic Treatment

Prophylactic treatment is indicated in all subjects with rheumatic cardiovalvular or with congenital heart disease, for they are the ones likely to contract bacterial endocarditis. Manipulations and operative procedures, especially dental extractions, tonsillectomy, cystoscopy, lithotomy or prostatectomy, are apt to inject organisms into the blood stream which lodge on a valve or blood vessel and form bacterial vegetations. Penicillin should be administered for twenty-four hours before and for forty-eight hours after the procedure. Dosage and duration are still experimental. Thill and Meyer[171] reported that penicillin given for fourteen hours before and for fifty-four hours after extraction of a tooth (in doses of 15,000 units every three hours) was inadequate to prevent the development of subacute bacterial endocarditis. It is more likely that the dosage was inadequate than that the duration of administration of penicillin was too brief. On the other hand 50,000 units intramuscularly every two hours in the twenty-four hours *preceding* dental extraction also failed to prevent bacteremia although it diminished its incidence.[60] It might be most practical to give 600,000 units of penicillin-procaine simultaneously with 500,000 units in saline, both intramuscularly one-half hour before the actual procedure, since the invasion of the blood stream is transient and occurs within a few minutes after the manipulation. Larger doses than the above may be required to prevent growth of resistant organisms. If there is obvious infection at the operative site, penicillin therapy should be begun several days before the procedure is performed.

Patients who are already suffering from bacterial endocarditis should be carefully examined for foci of infection. The necessary extraction of teeth or tonsils, drainage of sinuses or urologic procedures should be performed while the patient continues to receive active penicillin treatment.

PROGNOSIS

The outlook has dramatically improved since penicillin became available. Previously, at most, 1 to 4 per cent of the cases recovered spontaneously.[100, 102] With sulfonamides a somewhat greater number of cures were noted than previously—perhaps 5 to 6 per cent—with the outlook best in congenital cardiac cases, especially endarteritis associated with patent ductus arteriosus.

The percentage of cures of the infection is constantly increasing as larger series of cases are being reported and more adequate dosage and longer treatment are being administered. Through 1945, *elimination of the infection* was achieved in 107 (81.7 per cent) of 131 cases reported by six different groups of observers. At the present time it is probable that the infection can be controlled in about 90 to 95 per cent, if death does not occur before two weeks of treatment. In Wagner's[179] review of 469 cases of subacute bacterial endocarditis only 4.5 per cent were therapeutic failures due to the resistance of the organism. Since blood levels of 35 units per cc. of penicillin or more can be attained with huge doses of this drug combined with orally administered

caronamide, and since other antibiotics are available, it is probable that the number of resistant organisms causing bacterial endocarditis will become minimal.

On the other hand the *percentage of clinical recoveries* is smaller than the percentage of bacteriologic cures. Wagner[179] collected 371 reported recoveries (71.3 per cent) among 469 cases. Christie[23] collected 81 recoveries (55 per cent) among the first 147 unselected cases treated in Great Britain. Jones et al.[81] found reports of 266 recoveries (65.5 per cent) among 406 cases.

At first therapeutic failures were due chiefly to inadequate dosage and high resistance of the organism with consequent persistence of the infection. At present the most important cause of failure is delay in treatment.[100] Priest et al.[137] found that the average duration of the disease before the beginning of treatment was 9.2 weeks in a group of recovered cases and 22.5 weeks in a group of fatal cases. During the period of delay, progressive valvular damage and toxic vascular and inflammatory lesions of the heart muscle lead to irreversible heart failure, extensive vascular renal damage leads to uremia, or suppurative embolic lesions, suppurative pericarditis or deep-seated valvular or myocardial suppuration causes sudden death or uncontrollable infection. Thus the outlook becomes more and more favorable the earlier the diagnosis is made and adequate treatment begun.

Assuming that adequate blood levels of penicillin can be obtained to inhibit growth of the causative organism, there is no close relationship between the degree of sensitivity of the organism and the likelihood of recovery. The presence of complications before treatment is begun, such as heart failure, frequent and serious embolizations, suppurative pericarditis or ruptured valves, denotes a poor prognosis. Recovery may occur despite previous failures with penicillin, provided that the causative organism is sensitive to practical doses of antibiotics and no incurable complications have developed. Age and sex are usually insignificant for prognosis, but patients beyond the age of fifty are not as apt to recover as younger persons. Recoveries occur about equally when the disease complicates rheumatic or congenital lesions.

Relapses usually occur, if at all, in the first four weeks after discontinuing treatment. Rarely relapses seem to develop as late as three months afterward. Clinical and bacteriologic cure for six months after treatment almost always denotes permanent recovery from the given attack.

Cause of Death. In the fatal cases, death is most commonly due to congestive heart failure. This may develop during or after treatment. There has been some question as to the possible increase in frequency of heart failure in cases of subacute bacterial endocarditis since the advent of penicillin. With increased duration of life as a result of control of the infection, more of these patients may survive long enough to develop the clinical manifestations of heart failure. Rapid cure of extensively damaged valves may lead to the therapeutic paradox of increased valvular insufficiency and heart failure. On the other hand, Fiese's[47] experience led him to conclude that penicillin treatment has diminished the incidence of heart failure from 80 per cent to 30 per cent. It seems that the latter viewpoint is most likely, especially if treatment is begun relatively early.

Other causes of death are renal insufficiency and uremia, embolization, especially rupture of mycotic aneurysms of the cerebral vessels with sub-

arachnoid or cerebral hemorrhage, and persistent infection. Sudden death is uncommon but may be due to coronary or cerebral embolism or rarely to heart block with ventricular standstill, or to rupture of a splenic infarct.

ACUTE BACTERIAL ENDOCARDITIS

Definition. Acute bacterial endocarditis is an inflammatory disease of the endocardium, usually caused by pyogenic organisms. It is characterized by signs of a general infection (septicemia) with embolic or metastatic phenomena and, if untreated, terminates fatally within six weeks. It is distinguished from subacute bacterial endocarditis by a shorter duration, by different causative organisms and by differences in clinical and pathologic features. But the differentiation between acute and subacute bacterial endocarditis may be uncertain and both diseases may overlap with regard to all of the usual distinguishing features.

As in the subacute disease, the fundamental mechanism of acute bacterial endocarditis consists of (1) bacterial invasion of the blood stream, (2) localization of the bacteria on the endocardium, which is often the site of a previous abnormality, (3) persistent bacteremia, toxemia and embolization due to the bacterial vegetations on the endocardium. In order to avoid repetition, the following description of acute bacterial endocarditis is considerably abbreviated, special attention being directed to differences from the subacute form.

ETIOLOGY AND PATHOGENESIS

Causative Organisms. The acute disease is due most commonly to hemolytic streptococci, pneumococci or Staphylococcus aureus.[170] The hemolytic streptococci belong serologically to Lancefield's[92] Group A, but occasional instances due to streptococci of Group C or B following abortion or delivery have been reported.[143] Pneumococci responsible for acute bacterial endocarditis are usually aerobic but may be anaerobic.[75]

Among a variety of other organisms responsible for acute bacterial endocarditis are N. gonorrhoeae, N. meningitidis, E. coli, Pseudomonas aeruginosa (B. pyocyaneus), Klebsiella pneumoniae (Friedländer's bacillus), Actinomyces bovis, Micrococcus rugatus, spirilla and B. anthracis. Many of this latter group may produce either a subacute or an acute bacterial endocarditis.

Predisposing Causes. The presence of *previous valvular or congenital heart disease* is the most important predisposing factor in the acute as well as in the subacute disease. The bacterial vegetations are superimposed on a previous cardiac lesion in about 70 per cent of the cases. Because of the greater virulence of the causative organisms in this group, their transient invasion of the blood stream is more apt to result in a bacterial focus on normal valves than is a transient bacteremia with the less virulent organisms causing the subacute endocarditis.

In contrast with the subacute cases, acute bacterial endocarditis is almost always preceded by *some overt local or general infection* due to one of the above-mentioned causative organisms. This original infection may be active or apparently healed by the time the bacterial endocarditis is manifest. Sometimes bacterial invasion of the blood stream follows some operative procedure in an infected organ or tissue. In a considerable number of cases acute bacterial endocarditis, arising from some undetermined focus, is a terminal or terminating infection in the course of various chronic or fatal diseases such as cirrhosis

of the liver, leukemia, agranulocytosis, diabetes, nephritis and Libman-Sacks disease.

Age, sex and race do not appear to be significant factors. However, the age incidence in pneumococcal endocarditis appears to be ten to twenty years higher than that in endocarditis due to other organisms. This corresponds to the age incidence of pneumococcus pneumonia, which pneumococcus endocarditis generally follows. Acute bacterial endocarditis is not uncommon after the age of sixty, an important point to remember because this diagnosis is usually overlooked in elderly patients.[193] Gonococcal endocarditis is relatively more frequent in the colored race, presumably due to the higher incidence of gonorrhea.

PATHOLOGY

Heart. In the acute, as in the subacute form, the *vegetations* are the most striking feature. As in the subacute cases, they are usually superimposed on thickened, scarred, vascularized, rheumatic valves or on congenital cardiac lesions. The left side of the heart is chiefly involved. The pneumococcal and gonococcal infections are more apt to occur on previously normal valves, and affect the aortic valve more frequently than the other organisms. Vegetations on the right side of the heart are caused most often by the gonococcus, but even this organism is more apt to attack the mitral and aortic valves.

Ulceration is a feature of the acute cases, valvular destruction being especially severe in the pneumococcal and gonococcal cases. Because of the ulcerative process, *aneurysm* and *perforation* of the valves and loss of substance are more common in the acute cases than in the subacute cases. Vegetations are found on the mural endocardium much more rarely than in subacute bacterial endocarditis. The left auricle is uncommonly affected, but occasionally there are vegetations on the chordae tendineae and papillary muscles of the left ventricle. The interventricular septum and rarely the heart wall may be perforated.

Microscopically the vegetations are composed of solid bacterial masses or fibrinous material through which bacteria are diffusely scattered to the very surface of the lesion. In contrast with the subacute cases, blood platelets are infrequent, there are numerous polymorphonuclear leukocytes and the subjacent valvular tissue shows extreme necrosis and suppuration.[67] The bacteria extend into the collagenous structure of the valve. Healing is absent or minimal.

The heart muscle may show the acute or chronic lesions of rheumatic infection (with or without Aschoff bodies) in at least half the cases. In addition there are numerous focal lesions consisting either of myocardial submiliary or microscopic abscess or infiltrations of round cells and polymorphonuclear leukocytes. Abscess formation occurs particularly in the staphylococci or gonococcal cases.

Pericarditis is more common than in the subacute form. In addition to the pericardial lesions of a healed or active rheumatic endocarditis, in 20 to 40 per cent there is a purulent or sanguino-purulent pericarditis discovered at postmortem examination.

Other Organs. Pathologic alterations in other organs vary considerably in frequency, severity and kind according to the nature of the causative organism.

Splenic enlargement (acute splenic tumor) is usual.

The *kidneys* often present hemorrhages, infarcts and sometimes small or

large abscesses. There may be a focal or acute diffuse glomerulonephritis, the latter especially in the gonococcal cases.

The *liver* may disclose focal or diffuse areas of necrosis and degeneration.

Various lesions due to bacterial embolization or toxemia may be found in other organs. The staphylococcal cases may be characterized by widespread miliary or large abscesses, the "arterial pyemia" of Wilks.[189] Suppurative meningitis, seropurulent arthritis, cortical abscesses of the kidney or perinephric abscess may occur in fatal cases.

The *eye* may contain striking abnormalities. In contrast with the subacute disease, involvement of the uveal tract is not rare, and *panophthalmitis* may ensue. Hemorrhages occur in the retina, as well as Roth spots (more often than in subacute endocarditis). Optic neuritis may be present.

CLINICAL FEATURES

Acute bacterial endocarditis is not infrequently an accidental postmortem finding in a variety of acute or chronic infections and debilitating diseases whose symptoms obscured any clinical picture caused by the endocarditis itself. Often the endocarditis is a mere incident in a septicemia. The clinical picture is that of a general infection (septicemia) and differs in no way from that in septicemias without bacterial endocarditis. Therefore, to enumerate all of the symptoms of acute bacterial endocarditis would require a description of almost every type of bacterial infection. Symptoms of the endocarditis as such are recognized when the initial infection is unimportant or healed and the bacteremia has persisted for several weeks.

As in the subacute cases, the clinical features of acute bacterial endocarditis include: (1) general and toxemic, (2) embolic and vascular and (3) cardiac symptoms.

(1) The *general symptoms* are caused by the primary lesion and consequent bacteremia. In some cases these are responsible for all or nearly all of the symptoms. The *onset* is apt to be abrupt with fever and perhaps a chill. Sometimes the onset is indicated by a persistence or recurrence of fever when the initial infection has apparently healed. The general symptoms already mentioned include high fever of the intermittent or remittent type, chills, profuse sweats, marked weakness and various cerebral and psychic disturbances.

(2) The *embolic and vascular s*ymptoms consist of disturbances due to vascular occlusion in organ systems or in the extremities, and of cutaneous lesions which may be embolic or due to local vascular inflammation. The embolic phenomena vary according to the site affected. As in subacute bacterial endocarditis, infarctions of organs, meningitic or cerebral symptoms, and paralyses may result. They are less frequent and less prominent in the acute form, chiefly, I believe, because of the shorter duration of the disease. Infarctions when present are generally puriform and infected, unlike in the subacute cases. In the acute form, at least some of the petechiae are definitely embolic.

Cutaneous manifestations are frequent occurrences and are very important for diagnosis. They consist of petechiae, hemorrhages, erythematous, bullous and purulent lesions. There are *petechiae* with or without white centers, which may be elevated or not. Those with elevated centers are really miliary abscesses and are encountered in staphylococcus endocarditis. The *Janeway lesions* (p. 788) are almost pathognomonic, being seen in the subacute disease only occasionally, and in a less typical form. They are generally hemorrhagic in the

acute bacterial endocarditis. The lesions consist of inflammatory polymorphonuclear infiltrations of the walls of capillaries and neighboring tissue.

(3) Cardiac symptoms consist of organic murmurs due to previous valvular or congenital heart disease, of changes in the quality, intensity or radiation of murmurs previously present, or of the development of murmurs when previously absent.

Following are some of the features of the most common etiologic forms of acute bacterial endocarditis.

Streptococcus hemolyticus endocarditis is apt to arise in postpartum infections, septic abortions, infections of the throat, otitis media (when there is a complicating sinus thrombosis or meningitis), sinusitis (when there is a complicating osteomyelitis of the frontal, maxillary or sphenoid bones), genitourinary infections, cutaneous infections such as erysipelas or infected wounds. These infections first produce a bacteremia and subsequently an endocarditis. But only about 1 to 3 per cent of patients with Streptococcus hemolyticus septicemia develop a bacterial endocarditis;[162] these are usually patients with rheumatic or congenital cardiac lesions.

In the above circumstances bacteremia is usually denoted by the sudden onset of high fever, chills, sweats, prostration, delirium, etc.; a positive blood culture is confirmatory. In the presence of a valvular or congenital lesion it is probable that there is or will soon be a bacterial endocarditis. Petechiae, Janeway lesions, embolic phenomena and changes in murmurs develop with advanced endocarditis. They may and should be prevented by early and adequate treatment.

Staphylococcus aureus endocarditis usually follows an acute osteomyelitis, a furuncle, carbuncle or abscess, especially when the latter have been traumatized, and especially in diabetic patients. The endocarditis may develop after the passage of a catheter or cystoscope in the presence of a urinary infection. The clinical picture is characterized by an acute onset with chills and by high continued or intermittent fever. A positive blood culture is usually readily obtained. In the presence of a cardiac murmur, bacterial endocarditis is probable even before embolic manifestations, purulent pericarditis, metastatic pneumonia or abscesses, petechiae with raised white centers or splenomegaly are observed.

Pneumococcus endocarditis in the majority of cases follows lobar pneumonia, but occasionally other pulmonary diseases, pneumococcus arthritis or complications of pneumococcus otitis media.[123, 170, 147, 172] According to Lord,[111] pneumococcus endocarditis occurs in about 3 to 6 per cent of fatal cases of pneumonia but Osler[131] set the incidence as high as 15 per cent.

Like other complications of pneumonia, pneumococcic endocarditis develops late in the course of the disease or a few days after apparent temporary improvement and fall in temperature. Pneumococcic endocarditis should be suggested when, in the absence of empyema or extension of the pneumonic inflammation, fever persists or if there is a recurrence of fever after a temporary normal period. If careful examination of the heart is made, the finding of a cardiac murmur and persistent fever should strongly suggest pneumococcus endocarditis even before the blood culture is made.

As pointed out long ago by Netter,[123] meningitis develops in the majority of these cases. Unfortunately the diagnosis is often overlooked until meningitis or cerebral complications have appeared as a result of cerebral embolic and cerebral mycotic aneurysms. The triad of pneumococcus pneumonia, cardiac

murmur and meningitis is diagnostic of pneumococcic endocarditis. Pneumococcus arthritis and glomerulonephritis occur commonly. Effective antibiotic treatment requires that the diagnosis be made before this serious complication occurs. The diagnosis is justified on the basis of the recent history of lobar pneumonia, persistent fever, a cardiac murmur and the finding of a pneumococcus on blood culture, even if there are no embolic phenomena.

DIAGNOSIS

In acute bacterial endocarditis, the presence of a general infection is usually suspected, the problem in diagnosis consisting of the recognition of a concomitant endocardial infection. The dominant character of the disease and most of the individual symptoms may be caused by the septicemia alone even in the absence of endocarditis. The culture of organisms from the blood stream confirms only the diagnosis of a bacteremia. Petechiae are likewise not specific for endocarditis but the appearance of crops of white-centered petechiae in a patient with a proven bacteremia is almost always conclusive of a bacterial endocarditis. White-centered petechiae in the fundus have a significance similar to those in the mucous membrane or skin. Valvular defects, while suspicious, may be the result of previous disease. *Janeway lesions* are most significant for diagnosis. They should be specifically sought by examination of the palms and soles. A panophthalmitis in a patient with bacteremia suggests a bacterial endocarditis. For definite diagnosis of acute bacterial endocarditis in the presence of a bacteremia, one must observe the development of *new organic murmurs* or embolic major vascular closures.

However, since the availability of effective antibiotic agents, the absolute diagnostic proof of an acute bacterial endocarditis has become academic. The likelihood of acute bacterial endocarditis should be entertained whenever there is persistent fever in a patient with a cardiac lesion after the original infection has subsided, or whenever there is a septic course with chills, fever and sweats in such a patient. Frequent blood cultures are indicated when there is persistent fever in a cardiac patient whether or not a local wound or some other infection appears to account for the fever. If a positive blood culture is obtained and there is a suspicious organic cardiac murmur, the patient should be treated as if he has bacterial endocarditis, whether or not one can prove that the endocardium and not some other focus is the origin of the bacteremia.

TREATMENT AND PROGNOSIS

Penicillin, streptomycin and sulfonamides are as effective in the treatment of acute as of subacute bacterial endocarditis. However the need for early diagnosis and treatment is more urgent because without treatment a fatal termination is usual in two to six weeks, as compared to three to twelve months for the subacute cases.

Treatment should be started with a million units daily of penicillin after probable diagnosis on the basis of minimal criteria as described above and after an initial blood culture has been taken. The dosage may then be modified according to the organism grown in the blood culture and the sensitivity of the organism. Or, if necessary, streptomycin or other antibiotics are substituted. Further modification of dosage may be indicated by the clinical response as discussed under the subacute cases (p. 797).

The outlook depends largely on the speed with which treatment is instituted.

In a number of cases death occurs from heart failure or other complications after the blood stream and vegetations have been sterilized by penicillin. Wilhelm et al.[188] collected references to 40 patients with acute bacterial endocarditis treated with penicillin. Among 25 cases of Staphylococcus aureus endocarditis, 20 died and 5 recovered. Among 6 with pneumococcal endocarditis 4 died and 2 recovered and among 7 with hemolytic streptococcal endocarditis 5 died and 2 recovered. In one case of Staphylococcus aureus endocarditis, streptomycin in doses of 50,000 units every four hours for fifty-six days effected a cure after daily doses of 1 million units of penicillin had failed. Other results of treatment of isolated or small series of cases of acute bacterial endocarditis may be found in the reports of Harford et al.,[72] Dolphin and Cruikshank,[44] Glaser et al.,[61] Cataldo,[20] Myers,[120] and Scudder and Deputy.[157]

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35

SYPHILIS OF THE HEART AND AORTA

About 5 to 15 per cent of the cases of heart disease in this country and Great Britain were formerly attributed to syphilis,[20, 24] but this incidence has substantially diminished in recent years. With improved education, public health measures, and means of treating early syphilis, it is probable that cardiovascular syphilis will be encountered even less frequently.

Syphilitic heart disease is rarely a primary disease of the heart, resulting from gummatous or diffuse inflammatory lesions of the myocardium. In the vast majority of cases clinical syphilitic heart disease is secondary to syphilitic infection of the aorta (luetic aortitis) and its complications.

Syphilitic aortitis has been found at autopsy in more than 75 per cent of untreated cases of syphilis.[57] Clinically, however, evidence of cardiovascular involvement is observed in only 10 per cent of patients with late syphilis.[116, 8]

ETIOLOGY OF AORTIC SYPHILIS

Cause and Pathway of Infection

The organism responsible for cardiovascular syphilis is the Treponema pallidum (Spirochaeta pallida). The organisms enter the blood stream early in the disease, for excision of the chancre does not prevent the development of secondary and tertiary syphilitic lesions. The treponemata localize frequently in the ascending aorta but only very rarely in the myocardium. It is probable that the spirochetes reach the lungs where they are filtered out into the mediastinal lymph nodes. From there they are borne by retrograde extension into the perivascular lymph spaces around the vasa vasorum of the ascending aorta.[53, 68] The lymphatic spread of the microorganisms explains their predilection for the aorta and the rarity of endocardial and myocardial lesions, for the microorganisms do not attack the cardiovascular system from within the heart or great vessels.

The Latent Period. Between fifteen and twenty-five years often elapse between the onset of the primary syphilitic infection and the appearance of clinical manifestations of cardiovascular disease. This so-called latent period does not denote quiescence of the infection. It is more probable that progressive inflammation, tissue destruction and scar formation occur from the onset, but that

clinical symptoms and signs appear only when the aortic lesions are sufficiently severe and extensive or involve the coronary ostia and aortic valves.

Occasionally the latent interval is relatively short.[97] In a study of 142 individuals with syphilis of the aorta in whom the onset of the infection could be determined accurately there were 3 patients who developed clinical syphilitic aortitis within five years.[21] In rare instances syphilitic aortic aneurysm or insufficiency occurred within a year or two after the primary infection.[89, 94, 41] The appearance of clinical manifestations of cardiovascular syphilis should be regarded not as the beginning, but as the advanced stage of a protracted, progressive disease of the aorta.

Age and Sex. Syphilitic heart disease is most frequent between the ages of thirty-five and fifty-five.[126] However, acquired cardiovascular syphilis has been reported beyond the age of seventy and as early as twenty. Cardiovascular syphilis affects males predominantly in the ratio of between 2 to 1 and 5 to 1. This has been attributed to the higher incidence of primary syphilis among men, to the greater stress of their physical work, to greater indulgence in tobacco and alcohol and to constitutional differences. The higher incidence of coronary artery disease among males is also to be noted.

Other Etiologic Factors. There is a much higher incidence in this country among Negroes than among white individuals.[110, 17] It is probable that this is not due to racial differences but to the poorer economic and social status of the former. Among both groups syphilitic heart disease is encountered with increasing frequency the lower the social level and the greater the hardship.

Inadequacy of Early Antisyphilitic Therapy

Failure to treat early syphilis and inadequate treatment are prime factors in the occurrence of cardiovascular syphilis. Studies of patients with cardioaortic syphilis indicate that almost all of them had no antisyphilitic treatment at all or only sporadic inadequate therapy.[59, 22] Moreover comparative studies of the course of patients with and without completely satisfactory antiluetic therapy disclose a much lower incidence of cardiovascular syphilis in the properly treated group, although adequate treatment does not necessarily preclude cardiovascular complications.[52, 72]

Association of Cardioaortic Syphilis and Syphilis of the Central Nervous System

Straub's[111] emphasis on the frequent association of luetic aortitis with neurosyphilis was influential in demonstrating the syphilitic nature of the aortitis. In a report by Cole and associates,[22] there were 642 patients with cardiovascular syphilis, of whom 43 per cent also had syphilis of the central nervous system. Conversely, studies of patients with neurosyphilis have disclosed that a significant percentage have evidence of syphilitic aortitis and its complications.[40, 14]

Cardioaortic Disease in Congenital Syphilis

Aortitis, myocarditis, cardiac gummata and cardioaortic aneurysms have been reported in congenital syphilis.[127] Most of these were clinically insignificant, occurring in infants who died shortly after birth. Despite the frequency of congenital syphilis it rarely produces cardioaortic lesions of the type seen in acquired syphilis. In 4000 postmortem examinations at the Johns Hopkins Hospital, Norris[80] found only 2 instances of luetic aortitis which were presumably of congenital origin. McCulloch[73] found that only 3 of 32 syphilitics

dying before the age of two showed syphilitic cardiac lesions at autopsy. None of his patients up to the age of fifteen developed clinical evidences of cardiovascular syphilis. Recently Dominguez and associates[28] described clinical and postmortem observations on an eighteen year old girl with distinct signs of aortic aneurysm and aortic insufficiency caused by congenital syphilis.

PATHOLOGY OF CARDIOAORTIC SYPHILIS

The lesions of cardioaortic syphilis include those which originate in the aorta and those which arise directly in the myocardium. The former consist of luetic aortitis and its complications, namely insufficiency of the aortic valve, stenosis or occlusion of the coronary orifices and aortic aneurysm. The primary myocardial lesions are gummata and syphilitic myocarditis. The endocardium and pericardium are rarely involved and then only by extension of the above myocardial and aortic lesions.

Syphilitic Aortitis

Gross Pathology. The naked eye appearance of syphilitic aortitis is generally sufficiently characteristic to permit a definite diagnosis on gross examination. Often syphilitic aortitis is associated with atherosclerosis and calcification. The distinctive features are: (1) the bluish gray or porcelain-gray intimal plaques without atheroma or calcification; (2) the wrinkling and puckering of the inner aspect of the aorta with a tendency to form radial or parallel grooves, the latter in the direction of the long axis of the aorta; (3) the sharp transverse demarcation of the aortic lesions ending at the origins of the vessels of the neck, at the level of the diaphragm or at the origin of the renal arteries; (4) the localization of the most extensive lesions to the ascending aorta above the sinuses of Valsalva and the progressive diminution of lesions as one proceeds along the course of the transverse and descending thoracic aorta.

The wall of the aorta is irregularly thickened by the plaques and thinned out where it is grooved and puckered. It may be so thin that it becomes translucent. When the lesions are extensive, the aorta loses its elasticity and becomes widened and flaccid. This widening is irregular and may be localized particularly to the ascending aorta, or it may be diffuse. Rarely there is a gummatous type of aortitis.[33, 121] The isolation of virulent Treponema pallidum from the aorta of an individual with cardiovascular syphilis has recently been reported.[42]

Microscopic Pathology. *1. Adventitial Changes.* The primary lesion probably occurs around the vasa vasorum of the adventitia. There are perivascular infiltrations of lymphocytes and plasma cells and occasionally of epithelioid or histiocytic cells. The lumen of these small vessels becomes narrowed or obliterated by a proliferation of its intimal layer, which becomes fibrotic and elastified (endarteritis obliterans). There may be localized or diffuse inflammatory changes consisting of granulation tissue and round cells which form miliary gummata. The involved areas become replaced by scar tissue and by new vessels, both of which extend into the media.

2. Changes in the Media. The media has long been considered the site of the most prominent and most significant lesions,[26] whence the term, "productive mesaortitis,"[18] has been applied to this disease. It is probable that the medial lesions arise chiefly as a result of damage to the nutrient vasa vasorum and only in part through direct inflammatory changes in the media. The essential lesion is a necrosis of muscle and elastic tissue with the formation of scars

markedly distorting the architecture of this vessel layer. These scars are often of a stellate form. Throughout the media there is an infiltration of round cells, plasma cells and fibroblasts. The thinning of the aortic wall and its loss of elasticity are essentially due to the destruction of the medial layer, while the wrinkled, puckered appearance is the result of the contraction of scar tissue extending from the adventitia to the intima.

3. Intimal Changes. There are intimal thickenings consisting of scar tissue and elastic elements. There may also be scattered inflammatory cells and capillaries which have extended from the media. Unless there is associated arteriosclerosis, there is no lipoid or lime. However, atherosclerosis is frequently combined with syphilitic aortitis.

Nonsyphilitic Diseases of the Aorta

Inflammatory lesions of the aorta have been described by Siegmund[102] in a variety of infectious diseases, particularly scarlet fever, pharyngitis, subacute bacterial endocarditis. The aortic lesions of rheumatic fever have been described previously (p. 710). When extensive and severe, they may occasionally simulate syphilitic aortitis. Of special interest is the disease termed medionecrosis aortae idiopathica cystica.[31, 36] Microscopic examination reveals necrosis of the media with mucoid and cystic softening.[60] There is no inflammatory reaction but there may be evidences of healing with the formation of new connective tissue and occasional elastic fibers. The lesions are situated in the ascending aorta, and may lead to rupture of the aorta with dissecting aneurysm (p. 472), an incident often erroneously ascribed to syphilis.

Complications of Syphilitic Aortitis

1. Coronary Artery Stenosis and Occlusion. The most intense syphilitic aortic lesions are situated so close to the mouths of the coronary vessels that these orifices are frequently implicated in the disease process. The incidence of severe narrowing or occlusion of the coronary ostia in luetic aortitis is at least 15 to 25 per cent.[69, 16, 13, 46] By careful measurement with a calibrated metal cone inserted into the vessel openings, Bruenn[12] demonstrated that narrowing occurred in 33 per cent of his cases of luetic aortitis. That the coronary ostia are not involved even more frequently is due to the fact that they are usually located within the sinuses of Valsalva while the lesions of syphilitic aortitis tend to occur just above this level ("supravalvular sclerosis").[69] Not infrequently the coronary orifices have an anomalous origin higher up on the aorta, above the sinuses of Valsalva; in such instances they are almost always embedded within the syphilitic process. When the syphilitic process tends to extend downward so as to involve the commissures of the aortic valve, the incidence of severe coronary ostial stenosis or occlusion becomes very high. Thus, coronary ostial stenosis and occlusion are frequently associated with aortic insufficiency, a point worth remembering in interpreting clinical symptoms.

The mouths of the coronary vessels become narrowed by encroachment of the raised intimal plaques upon their margins or by extension of the aortic syphilitic process into that portion of the coronary artery lying within the aortic wall, with subsequent contraction of resulting scar tissue. Stenosis of either one or both orifices may occur and complete occlusion is not rare.[15] The syphilitic process rarely, if ever, extends beyond the aortic openings into the vessels them-

selves, and then only for 1 to 2 cm.[77] But aneurysms of the proximal portion of the coronary arteries have been reported.[103, 101]

Despite the relative frequency of syphilitic coronary stenosis or occlusion, resulting myocardial infarction is rare.[13, 67] In a series of 185 cases of myocardial infarction only 3 were due to syphilitic coronary ostial occlusion.[13] These 3 cases were found in a series of 193 showing luetic aortitis at autopsy, 40 of them with coronary ostial stenosis. On the other hand Love and Warner,[65] in a study of 15 cases with coronary ostial stenosis, found 8 with pronounced fibrosis of the myocardium and 4 with acute myocardial infarction. Rarely, sudden death in cases of luetic aortitis is due to coronary embolism of one main artery arising in an associated atheromatous mural thrombus, while the other coronary ostium is narrowed by the syphilitic process.[86]

2. Syphilitic Aortic Insufficiency. Aortic insufficiency is the result of an extension of a luetic aortitis to the valve commissures and cusps and not of direct valvular involvement. At postmortem examination, aortic insufficiency is found in 20 to 35 per cent of cases of luetic aortitis.[19, 69]

The earliest, the most significant and the most diagnostic gross anatomic feature of luetic aortic insufficiency is the widening of the commissures of the aortic valves.[96] This is the chief factor in the production of insufficiency. It is probably due to necrosis, scarring and consequent dilatation of the aortic ring.[35] The commissural spaces between the cusps may become as wide as 0.5 to 1 cm. The free margin of the cusps may be everted, rolled and retracted, and the cusp itself stiffened and shortened. This shortening and retraction is a second factor contributing to lack of coaptation of the cusps and resulting regurgitation. According to Jason[45] two processes account for syphilitic distortion of the aortic valve: (a) a destructive inflammation of the aortic wall resulting in destruction and dislodgement of the cusp attachments at the commissures, and (b) reparative fibrosis. The margins of the aortic cusps may become attached to the aortic wall but they do not become attached to each other. Thus aortic stenosis does not occur in syphilis unless rheumatic valvulitis or calcification of the cusps is associated. The combination of rheumatic and syphilitic aortic valvular disease has been documented.[93, 113, 63] Bacterial endocarditis rarely complicates syphilitic aortic insufficiency[11] unless there are associated rheumatic lesions.[54]

Rarely there is an extension of the syphilitic aortitis by way of the annulus fibrosus not only to the aortic valve but also to the anterior mitral cusp[106] and to the septum fibrosum.[6, 104]

The heart itself becomes considerably enlarged due to dilatation and hypertrophy of the left ventricle,[78] especially its outflow tract.

3. Aortic Aneurysm. Aortic aneurysm is a complication resulting from a severe and extensive luetic aortitis. It has been found at autopsy in 10 to 30 per cent of cases of luetic aortitis. In Martland's[69] series dealing with cases of sudden death, it occurred in 38 per cent of the cases of cardiovascular syphilis. The aortic wall becomes weakened as a result of the destruction of muscle and elastica in its medial layer. When this is extensive and severe, the continued blood pressure with its systolic accentuation serves gradually to dilate the vessel. When there is a pronounced localized dilatation, a saccular aneurysm is formed.

Saccular aneurysms may be multiple or single. They most frequently involve

the ascending aorta, less often the arch, the descending and abdominal aorta, in that order of incidence. The aneurysmal sac may be filled with laminated thrombus, which sometimes occludes a small perforation and on rare occasions is the origin of emboli. The great danger of aneurysm is perforation, but most of the symptoms, when present, result from pressure on neighboring vital structures. The pressure may be great enough to erode bone.

Syphilitic Myocarditis

Primary syphilitic disease of the myocardium was classified by Virchow[117] into the gummatous and fibrous varieties. The fibrous lesions are nonspecific and there is doubt that they represent a distinct form of syphilitic myocarditis.

Primary syphilitic myocarditis is uncommon and is confined to gummatous lesions. The frequency of syphilitic lesions and spirochetes in the myocardium, reported by Warthin,[119] has not been substantiated.[95] There may be localized gummata or a diffuse gummatous myocarditis. In a recent report, Sohval[105] was able to collect 97 authentic cases of cardiac gummata and only 7 of diffuse gummatous myocarditis. The great majority of gummata occur at the base of the left ventricle and of the interventricular septum.[109] Gummata situated in the interventricular septum may involve the bundle of His or one of its branches.[66] A gumma may result in cardiac aneurysm, may lead to rupture of a papillary muscle or of the heart wall, or rarely occludes a valvular orifice.

The diffuse gummatous myocarditis consists essentially of miliary or submiliary gummatous lesions with syphilitic granulation tissue and eventual scarring. While these lesions are rare, they occasionally produce a distinct clinical picture, e. g., one resembling acute myocardial infarction in a case reported by Reifenstein.[90]

CLINICAL FEATURES

Uncomplicated Syphilitic Aortitis

Symptoms. Syphilitic aortitis is an asymptomatic lesion.[51, 71, 29] The symptoms attributed to it[70] are probably all due to its complications—coronary ostial stenosis, aortic insufficiency or aneurysm—or to associated coronary arteriosclerosis.

Physical Signs. It is questionable whether there are distinctive physical signs of uncomplicated luetic aortitis. A *loud bell-like or tambour-like second aortic sound* (bruit de tabourka) has been described as characteristic.[44] However, it may be absent and a similar sound is frequently heard in cases of hypertension and aortic arteriosclerosis. Similarly, a rough, *aortic systolic murmur* may be due to syphilitic or arteriosclerotic changes and dilatation of the ascending aorta. Both of these signs may be suggestive of syphilitic aortitis if they occur in subjects under forty with a positive serologic reaction for syphilis and without hypertension or any other disease that may cause aortic dilatation.

Coronary Stenosis or Occlusion

The clinical features of coronary ostial stenosis or occlusion sometimes cannot be separated from those of the commonly associated aortic insufficiency.

The slow progression of ostial stenosis permits the development of an extensive collateral circulation chiefly through extracardiac anastomoses.[91]

Hence there are frequently no symptoms referable to coronary ostial stenosis, even when the stenosis is severe and involves both main arteries.

As a rule severe coronary ostial stenosis is characterized by *angina pectoris*[83] indistinguishable from that due to advanced coronary arteriosclerosis, except that it appears at a relatively earlier age. The clinical picture of acute myocardial infarction is seen rarely. *Sudden death* from ostial stenosis or atresia is not infrequent. By causing relative myocardial anoxia, and not infrequently myocardial fibrosis, coronary ostial narrowing may induce or contribute to the development of heart failure, especially when the size and work of the heart are increased by a concomitant aortic insufficiency.

Syphilitic Aortic Insufficiency

Cardiac pain and dyspnea are the most frequent symptoms associated with syphilitic aortic insufficiency. However, the cardiac pain is probably most often due to coronary ostial stenosis. In Bruenn's[12] series of 39 cases of the latter, 34 (87 per cent) revealed simultaneous aortic insufficiency. The infrequency of cardiac pain in rheumatic aortic insufficiency has been mentioned.

For relatively long periods cases of syphilitic aortic insufficiency may be well compensated. But even during this stage there may be palpitation, pounding in the ears or uncomfortable pulsations in the head and neck.

Left-sided heart failure probably develops not only because of the strain of the aortic valvular insufficiency, but also because the development of coronary ostial stenosis prevents the increased blood flow required for the nutrition and work of the hypertrophied heart. This is analogous to the development of heart failure in compensated rheumatic aortic insufficiency, when arteriosclerosis narrows or occludes the coronary arteries. In syphilitic patients beyond the age of fifty coronary arteriosclerosis as well as ostial stenosis may be an important factor in inducing both angina pectoris and congestive heart failure.

Paroxysmal dyspnea, especially at night, is an early and frequent symptom[64] ("syphilitic asthma"). Exertional dyspnea is also an early symptom of left ventricular failure in syphilitic aortic insufficiency. Sooner or later orthopnea, cough and weakness are associated. Attacks of acute pulmonary edema are not uncommon. Within a few years frank evidences of right-sided failure also appear.

The physical signs of aortic insufficiency have been described (p. 593).

Aneurysm of the Aorta

Aneurysm of the aorta may remain asymptomatic for many years up to the final blowout. Symptoms occur as a result of pressure on neighboring organs or of perforation. The perforation is usually into the pericardial or left pleural cavity, the left bronchus, the esophagus or trachea, and occasionally into the right pleural cavity, right bronchus, the superior vena cava, pulmonary artery or externally.[9] Aneurysms of the sinus of Valsalva usually perforate into the right atrium and ventricle. Sudden death is common.

Aneurysm of the Ascending Aorta and the Aortic Arch. Aneurysms of the ascending aorta have been distinguished as "aneurysms of physical signs" in contrast to those of the arch which are termed "aneurysms of symptoms." The ascending aorta is most frequently involved and is most apt to be associated

with syphilitic coronary stenosis and aortic insufficiency. Since the ascending aorta is entirely within the pericardial sac, rupture occurs most frequently into that cavity. As it enlarges, the aneurysm usually extends anteriorly upward and to the right, compressing the right bronchus and lung, the superior vena cava and the second or third ribs to the right of the sternum. Occasionally it produces pulmonary stenosis by compressing the pulmonary artery.[25] It may attain enormous bulk and appear as a visible tumor in the first or second right interspace near the right sternoclavicular joint. Occasionally such a visible tumor may be seen oozing blood from a superficial erosion, and rarely the aneurysm ruptures externally.

Aneurysms of the arch usually compress the trachea, the esophagus, the left bronchus, the left recurrent laryngeal nerve and the sympathetic nerves. When the aneurysm is essentially confined to the arch, pressure on these structures is likely to produce symptoms quite early. Patients with this lesion often first consult the laryngologist, the gastroenterologist or the specialist in pulmonary disease.

Symptoms. Chest pain and *cough* are the commonest complaints. The pain is often persistent and may be due to pressure of the aneurysmal sac on adjacent nerves or to the erosion of bone. The cough, which is dry at first and may have a brassy quality, results from pressure on the trachea or main bronchus. The brassy quality is ascribed to involvement of the recurrent laryngeal nerve. Later in the disease the cough is associated with expectoration, and more rarely with hemoptysis. These are due to bronchostenosis and secondary infection with resulting atelectasis and bronchiectasis. The clinical picture produced has been termed aneurysmal phthisis.

Pulmonary and pleural symptoms may actually dominate the clinical picture of aortic aneurysm.[50] Atelectasis, bronchopneumonia, abscess or bronchiectasis may arise not only from tracheal or bronchial compression but also from direct invasion of the lung by the aneurysm. Tuberculosis may be associated. Pleural complications arise as a result of rupture into the pleural cavity, compression of the pulmonary or azygos veins, or extension of pulmonary infection to the overlying pleura.

Dyspnea is due to pressure on the trachea or on a bronchus. Inspiratory stridor may develop. *Hoarseness* results from paralysis of the left recurrent laryngeal nerve. *Hemoptysis* may result from erosion of the trachea, bronchus or pulmonary tissue or from bronchiectasis due to stenosis of a bronchus with secondary infection. *Dysphagia* is due to partial obstruction of the esophagus. When there is pain on swallowing, it is probable that the esophageal mucosa has been eroded by the aneurysm. Rarely, pressure on the phrenic or sympathetic nerve produces symptoms such as hiccup, diaphragmatic paralysis or unilateral absence of sweating of the face.

Physical Signs. The signs are essentially those of an expanding, pulsating, mediastinal tumor. Inspection and palpation may reveal a pulsation in the anterior chest wall in the second or third right interspaces, occasionally higher up, or to the left. Rarely a bloody tumor mass is visible on the chest wall. There may be inequality of the pupils with dilatation of the right due to pressure on the cervical sympathetic chain. Occasionally, unilateral exophthalmos also results. Suffusion of the face, neck and upper extremities with cyanosis and edema may be produced by pressure on the great veins. The edema and cyanosis

may be localized to the right arm if the pressure is confined to the subclavian vein, but this is rare.

A systolic thrill and a *diastolic shock* may be palpated over the mass. As a result of pressure of the aneurysm on the bronchi, a *tracheal tug,* synchronous with the heart beat, may be felt as a downward pull at the thyroid or cricoid cartilage. There may be an *inequality of pulses;* usually the right one is diminished in amplitude, delayed or obliterated by partial interclusion of the orifice of the innominate artery or aneurysmal involvement of that vessel itself. There is a corresponding difference in blood pressure in the two arms.

The heart is not enlarged as a result of aneurysm itself. Systolic murmurs are often present over the aneurysm. Diastolic murmurs are due to associated aortic insufficiency.

Distinctive features, permitting a clinical diagnosis, appear when an aneurysm of the aorta perforates into the pulmonary artery[85, 79, 98] or into the superior vena cava,[3, 99] or when an aneurysm of the sinus of Valsalva perforates into the right atrium[39] or ventricle.[38] There is a loud continuous bruit with systolic accentuation and a palpable thrill, as in arteriovenous fistulas. Cardiac enlargement, electrocardiographic signs of right ventricular strain and congestive heart failure appear quickly and usually lead to a rapid end. Perforation into the superior vena cava is disclosed also by cyanosis and edema of the face and neck. In instances of perforation into the right atrium there may be visible double pulsations in the jugular veins resembling those of tricuspid stenosis. While aneurysms of the sinus of Valsalva are most often due to syphilis, they may also be due to bacterial endocarditis and occasionally to a congenital malformation.

Aneurysm of the Descending Aorta. Because of their location, aneurysms of the descending aorta may reach immense size and may almost completely fill the left thoracic cavity before they produce symptoms either by pressure on neighboring organs or by perforation. One is often surprised to find a huge thoracic mass on roentgenologic examination of a patient who has complained of few or no symptoms.

As with aneurysms of the arch, the chief symptoms are chest pain, dyspnea and cough. Pleural effusion, hydrothorax and hemothorax rarely develop. Dysphagia is an occasional symptom resulting from pressure on the esophagus. An important sign of a large aneurysm of the descending aorta, and one often overlooked, is a visible pulsation on the posterior chest wall either below and to the left of the left scapula or somewhat higher in the interscapular region.

Aneurysm of the Abdominal Aorta. Aneurysms of the abdominal aorta are generally considered to be predominantly arteriosclerotic, syphilis being responsible for only 9 per cent in the series reported by Mills and Horton.[75] However, in other collected series of abdominal aneurysms, in which there were more Negroes and somewhat younger individuals, syphilis was responsible for 50 to 80 per cent of the cases.[48, 43] Syphilitic aneurysms occur predominantly in subjects below the age of fifty and almost exclusively below the age of sixty.[100] Arteriosclerotic abdominal aneurysms occur predominantly in subjects beyond the age of sixty and almost never before fifty. The syphilitic aneurysm usually occurs at the level of the celiac axis.

The *commonest symptom* of syphilitic abdominal aneurysm is pain in the abdomen or back. It may be paroxysmal, or constant and boring. There may be

root pains radiating from the back to the upper abdomen. These and other symptoms result from erosion of the vertebrae, pressure on the spinal cord, gastrointestinal tract, ureter or other abdominal structures. Death is usually caused by rupture of the sac into the peritoneal cavity, gastrointestinal tract or retroperitoneal space. Most abdominal aortic aneurysms are asymptomatic.

Examination may reveal an expansile pulsating mass, palpable thrill, and audible bruit, and occasionally a difference in the femoral pulsations. Roentgenologic examination may disclose an abdominal mass with or without calcification and erosion of the anterior vertebral bodies from the eleventh thoracic to the second lumbar.

Gummata of the Heart and Gummatous Myocarditis

Cardiac gummata and gummatous myocarditis usually produce no clinical picture. Rarely, a gummatous aneurysm may perforate into the pericardium and result in sudden death. A gumma may interfere with conduction along the bundle of His or its branches, and produce either heart block or bundle branch block.[66] Gummata at the base of the left ventricle or the interventricular septum may protrude into the valvular regions, producing a pseudostenosis.[105, 66] The pulmonic and aortic valves are involved in that order of frequency and, much more rarely, the mitral and tricuspid. The resulting clinical picture is usually difficult to interpret, the essential signs being rough systolic murmurs of unusual quality and situation, occasionally a palpable thrill and unexplained roentgen ray shadows at the cardiac borders.

Arrhythmias and Electrocardiographic Changes in Luetic Aortitis and its Complications

Arrhythmias are infrequent in cardiovascular syphilis. Premature beats are the most common abnormality. Occasionally there is auricular fibrillation.

Electrocardiographic changes present no specific pattern and usually occur in cases with aortic insufficiency and coronary ostial stenosis. Evidence of left ventricular strain and alterations in the R-T segments, negative T waves in leads I and II and widening and notching of the QRS complexes are most frequently observed.[12, 47, 23] Occasionally there is a pattern resembling that of anterior wall infarction. In a syphilitic patient below the age of forty-five, changes in the ST segments and T waves following an exercise test suggest the presence of coronary ostial stenosis.[5] Prolongation of the P-R interval, bundle branch block and complete heart block are infrequent findings in cardiovascular syphilis. Among older individuals with cardiovascular syphilis, an associated hypertension or coronary sclerosis is often responsible for the electrocardiographic changes.

DIAGNOSIS OF CARDIOAORTIC SYPHILIS

Roentgenologic Diagnosis of Cardioaortic Syphilis. The roentgenologic diagnosis of uncomplicated syphilitic aortitis[107] has been based on the finding of widening or dilatation of the ascending aorta in patients below the age of forty, who have definitely had syphilis, but are free from other conditions which may cause aortic dilatation. In persons above the age of forty aortic arteriosclerosis is very common and may produce similar dilatation. However, the arteriosclerotic aorta is more elongated than widened, and the aortic knob extends toward the left sternoclavicular junction. Furthermore in the left oblique position the widened syphilitic aorta usually encroaches on the aortic window,

while the elongated arteriosclerotic aorta forms a large convex arch with a more spacious window.

Variations in the normal range and difficulties in measurement prevent the accurate diagnosis of lesser degrees of aortic widening. If the esophagus contains barium, the width of the aortic arch can be measured, in the lateral view, at the level where the aorta makes a meniscus-like impression on the esophageal wall.[56] Normally this is less than 3 cm. and should not exceed 4 cm. Occasion-

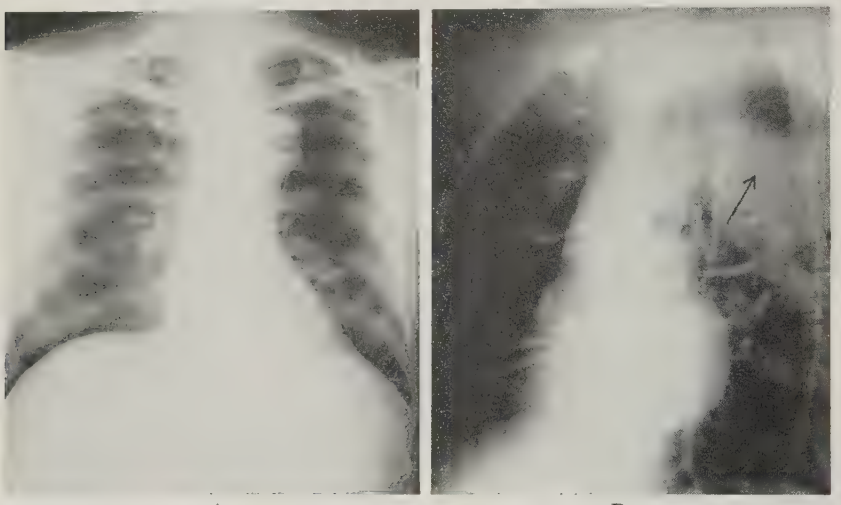


Fig. 71. Syphilitic aneurysm of ascending aorta.

ally the width of the aorta can be measured fairly accurately when its boundaries are outlined by the deposition of lime. In practice, the presence of aortic dilatation is often suggested when the right supracardiac border becomes distinctly convex and protrudes as far to the right or further than the right cardiac border formed by the right atrium. When syphilitic aortic dilatation is easily recognizable, it is a question of definition whether we are dealing with uncomplicated aortitis or with aneurysm.

Sacculated aneurysms of the aorta appear as rather sharply defined semicircular or convex projections from the mediastinal region into the lung fields (Fig. 71). On fluoroscopy these shadows cannot be separated from the vascular pedicle when the patient is rotated in different positions and they may pulsate. However, too much emphasis should not be placed on the diagnostic value of

pulsation, since it is often absent, especially if the aneurysm is very large. Furthermore some tumors may appear pulsatile because of pulsations transmitted from the heart or great vessels. Aortic aneurysms may compress and displace the esophagus, trachea or bronchi. An aneurysm of the aorta arising in the sinus of Valsalva is usually impossible to recognize unless it is of considerable size or displaces the pulmonary artery or right atrium. Albrecht[1] and others[81] have described the recognition of such aneurysms, especially those arising in the right aortic sinus. The smooth, oval or circular shadow of an aneurysm of the abdominal aorta may be delineated more clearly following the induction of pneumoperitoneum injection of air into the colon, or by administering a seidlitz powder. Erosion of the upper lumbar vertebrae or of their transverse processes may be seen, especially in lateral views.[10] In aneurysms of the thoracic aorta there may be concave erosions of the ribs or sternum as well as of the



A B

Fig. 72. *A*, Syphilitic aneurysm of arch of aorta, presenting on left side.
B, Angiocardiogram of same. Aneurysmal mass continuous with aorta and extending posteriorly (Arrow).

vertebrae. Pleural or pulmonary abnormalities and rarely paralysis of one leaf of the diaphragm may be observed as a result of pressure of the aneurysm on neighboring structures.

Angiocardiography has greatly facilitated the diagnosis of aortic aneurysms and especially their differentiation from mediastinal tumors[108, 112] (Fig. 72).

The roentgenologic findings in aortic insufficiency have been described elsewhere (p. 595). Coronary ostial stenosis, per se, induces no radiologic abnormalities.

Diagnosis of Uncomplicated Aortitis. This is a difficult diagnosis and its criteria are not well defined. It may be considered when there is radiologic evidence of dilatation of the aorta in a patient who is below the age of forty, has definitely had syphilis and is free from hypertension or rheumatic valvular disease. Accessory diagnostic findings may include a hollow or bell-like accentuated aortic second sound and an aortic systolic murmur. In patients beyond the age of forty, but with all the other findings, the diagnosis may be aortic arteriosclerosis or syphilitic aortitis.

Diagnosis of Syphilitic Coronary Ostial Stenosis or Occlusion. This may be considered in a patient with the above evidence of syphilitic aortitis, or with evidence of syphilitic aortic insufficiency, who also suffers from angina pectoris. Even under these circumstances the cardiac pain may be due to a concomitant coronary arteriosclerosis, especially in patients beyond the age of fifty. In the absence of other evidence, angina pectoris is almost always due to coronary arteriosclerosis and not to syphilitic ostial stenosis, even when the Wassermann reaction is positive.

Diagnosis of Syphilitic Aortic Insufficiency. This diagnosis has been discussed in the chapter on aortic insufficiency. The syphilitic etiology of the valvular lesion is indicated by evidence of syphilis, absence of a history of rheumatic fever or of a cardiac murmur in childhood, absence of mitral stenosis, and by the presence of a systolic and diastolic murmur, loudest in the second right interspace. The association of both syphilitic and rheumatic valvular disease has been noted.[93, 62] In rare instances of syphilitic aortic insufficiency associated with a congenital interatrial septal defect, the diagnosis may be suggested by the combined evidence of syphilitic aortic insufficiency and right axis deviation in the electrocardiogram, auricular fibrillation and distinct dilatation of the pulmonary arteries.[61]

Diagnosis of Syphilitic Aortic Aneurysm. This is essentially a radiologic problem (p. 825). Occasionally there is a visible or palpable pulsating mass in the first or second right interspace or in the left scapular region. The possibility of aortic aneurysm should be considered in any patient who has definitely had syphilis and who suffers from chest pain, dyspnea, cough, especially a brassy cough, hoarseness, severe abdominal pain, or paralysis of the recurrent laryngeal nerve. The value of contrast angiocardiography has been mentioned.[108, 112]

DIFFERENTIAL DIAGNOSIS

Syphilitic ostial stenosis must be differentiated from the much more frequent coronary arteriosclerosis. The problem of distinguishing rheumatic from syphilitic aortic insufficiency has been discussed. Aneurysm of the thoracic aorta must be differentiated from bronchopulmonary neoplasms or infections, mediastinal tumors, pericardial effusions, lesions of the larynx and congestive heart failure. Roentgenologic examination of the chest, and angiocardiography if necessary, usually provide the necessary diagnostic data to distinguish these varied lesions. Bronchoscopy and esophagoscopy are contraindicated when aortic aneurysm is suspected because of the danger of hemorrhage.

The Wassermann Reaction in Cardiovascular Syphilis. The blood serologic reaction for syphilis as obtained by the Wassermann, Kahn or similar procedures is reported positive in 75 to 95 per cent of the cases.[17, 22, 4] This indicates that in about 15 per cent of the cases of cardiovascular syphilis the serologic reaction may be negative. However, caution should be exercised in making such a diagnosis when the serologic reaction is negative unless the other diagnostic criteria are unequivocal. In 342 cases of cardiovascular syphilis in which the spinal fluid was studied by the Clinical Cooperative Group,[22] significant abnormalities were found in 56 per cent. Thus evidence of syphilis of the central nervous system should suggest a careful search for cardiovascular lues and vice versa.

PROGNOSIS

In a large percentage of cases of cardiovascular syphilis evidence of this disease is a coincidental finding at autopsy. Of 1040 instances of cardiovascular

syphilis studied at necropsy by Welty[122] the syphilitic lesion was a direct or important contributing cause of death in only 339 cases. Similarly the favorable course of uncomplicated syphilitic aortitis is suggested by the fact that this lesion is found post mortem in a large majority of persons with longstanding syphilis of whom only 5 to 10 per cent have had clinical evidence of the disease.

But even among those who eventually develop clinical evidence of cardiovascular syphilis there is an asymptomatic stage of considerable duration. According to the studies of syphilitic aortic insufficiency reported by McDermott[74] and associates this asymptomatic phase varies between two and ten years, with an average of six years. Similarly Hubert[44] reported that of 137 patients with syphilitic aortitis 47 were completely free of symptoms after six and a half years; and Reader et al.[87] found 16 of 27 patients with syphilitic aortic insufficiency who were asymptomatic and mostly working, after five years of observation. The existence of a long asymptomatic period is suggested by the finding of virtually complete closure of both coronary ostia in the hearts of individuals who were asymptomatic and at work until a relatively brief period before death. It is also remarkable how often an aortic aneurysm reaches enormous size before it produces symptoms.

The further course and duration of life after the onset of symptoms is quite variable. It was formerly stated that this symptomatic phase was an ominously progressive one with death in one to three years. However, even Grant[34] found that the case fatality rate in syphilitic aortic insufficiency was only 64 per cent after ten years. Kampmeier and Coombs,[49] in a study of the records of 163 patients with syphilitic aortic insufficiency, found that about 55 per cent died in the first three years after the onset of symptoms; 20 per cent died in three to twelve years; while the remainder were still alive, almost half of them, for an average period of ten years. The duration of the symptomatic phase in the group of patients with syphilitic aortic insufficiency studied by Reader et al.[87] varied between two and fourteen years with an average of 5.6 years. Although Woodruff[125] found that two thirds of the patients in his series of cases died within two years of the onset of symptoms, a similar percentage survived the age of fifty and a considerable number died between the ages of sixty and seventy.

In general the outlook for uncomplicated syphilitic aortitis is much better than for cases with aortic insufficiency, aneurysm or coronary ostial stenosis. The outlook becomes distinctly more ominous when subjective symptoms appear, especially angina pectoris and those due to congestive heart failure or to aneurysmal compression of vital structures. In the presence of heart failure the mortality rate increases substantially and the duration of life averages two to three years. However, 9 of 30 surviving patients studied by Reader et al.[87] had suffered from congestive heart failure three to nine years previously and had responded to treatment. In cases of luetic aortitis complicated either by aneurysm, coronary ostial stenosis or aortic insufficiency there is always the danger of sudden death.[69, 58] The prognosis is worse in Negroes than in white patients. Patients engaged in occupations involving arduous physical exertion have a relatively unfavorable outlook.

Relation of Antisyphilitic Treatment to Prognosis. The prognosis of cardiovascular syphilis is dependent also on the administration of antisyphilitic treatment. It is generally believed that adequate early treatment of syphilis greatly reduces the incidence of luetic aortitis and of its serious complica-

tions.[22, 118, 114, 72] On the other hand, there is less certainty as to the effectiveness of antisyphilitic therapy given after the clinical recognition of syphilitic aortitis. However, the studies of Padget and Moore[82] and the cooperative clinical report of Cole et al.[22] suggest that after regular adequate treatment of cardiovascular syphilis with an arsenical and a heavy metal, the mortality rate during the period of treatment was substantially lessened, and the duration of life was two to five times as great in the treated group as in the untreated.

TREATMENT OF CARDIOVASCULAR SYPHILIS

Prophylaxis. Available data indicate that cardiovascular syphilis may be largely prevented by prompt case finding and adequate treatment and observation of early syphilis.[30] Unfortunately it is difficult to define adequate treatment since our concepts in this regard are now in a state of flux. Formerly, adequate treatment was believed to consist of at least twenty injections of an arsenical and twenty injections of bismuth administered regularly over a period of two years. The effectiveness of concentrated shorter courses and of penicillin remain to be evaluated after a prolonged follow-up period. Aside from other advantages, treatment with penicillin over a period of eight to fourteen days is more likely to encourage the cooperation of the patient and completion of the course of therapy than previous prolonged schedules with other drugs.

Specific Therapy. The aim of specific therapy in cardiovascular syphilis is to relieve the patient's symptoms and prolong his life without undue risk. Specific therapy is given because cardiovascular syphilis denotes a persistently active inflammatory lesion which, it is hoped, can be controlled by antiluetic drugs. In a pathologic study of 45 treated and untreated cases of syphilitic aortitis, Webster and Reader[120] found persistent syphilitic inflammatory activity in all of 19 untreated cases and in only 3 of 19 adequately treated ones. While antisyphilitic therapy may control the active inflammation, it cannot be expected to alter significantly certain irreversible lesions due to necrosis of muscle and elastic tissue and scar formation.

On the other hand the ordinary risks of serious reactions due to antisyphilitic drugs may be greatly enhanced in the patient with cardiovascular syphilis. This refers particularly to the major and often fatal reactions following the injection of an arsenical drug, but also to the "minor" nitritoid crises. In addition, all forms of specific antisyphilitic therapy are often followed by a Jarisch-Herxheimer reaction or therapeutic shock, characterized by fever in the first twelve to twenty-four hours of treatment and often by an exacerbation of the syphilitic lesion. This reaction may be serious in patients with coronary ostial stenosis, since it may be accompanied by increased swelling of the tissues with further stenosis or occlusion. This may be denoted clinically by cardiac pain or even sudden death. Occasionally antisyphilitic therapy is followed by a therapeutic paradox.[124] After a brief period of improvement, the patient's condition deteriorates and he may develop evidence of ostial stenosis, aortic insufficiency or heart failure. Presumably healing of a syphilitic lesion with increased scar formation produces or intensifies the aortic valvular or coronary ostial lesion. The therapeutic paradox is rare. It is not amiss to emphasize that no physician should undertake the treatment of syphilis, whether of the cardiovascular system or other forms, without a thorough knowledge of the toxic effects of the antisyphilitic drugs.

Although treatment schedules are useful as a guide, it is important to indi-

vidualize therapy according to the age of the patient, previous treatment, character of the syphilitic lesion, functional disturbance, symptomatology, the presence or absence of associated disease and the response to drugs administered. Antisyphilitic drugs must be given much more cautiously than in the treatment of early syphilis. Bed rest is often essential at the commencement of treatment in cases of aneurysm, aortic insufficiency or coronary ostial disease, if there are clinical symptoms. Antisyphilitic drugs should be discontinued if symptoms appear or become intensified during treatment.

Specific Antiluetic Drugs. Bismuth has been the mainstay in the treatment of cardiovascular syphilis. The slow absorption of the oil-insoluble preparations is an advantage in the commencement of treatment.

Mercury has been generally superseded by bismuth.

Potassium iodide is frequently administered orally simultaneously with other drugs, but its value is uncertain.

According to some authorities the *arsenicals* are not to be administered at all in cardiovascular syphilis, while others greatly delimit their indications. Old arsphenamine should never be given. All arsenical preparations are contraindicated in the presence of angina pectoris or other evidence of coronary insufficiency, and in the presence of advanced or symptomatic aneurysm. All specific antiluetic therapy, bismuth as well as arsenical, is contraindicated in the presence of heart failure.

Penicillin. The dosage of penicillin has not yet been standardized and its usefulness in cardiovascular syphilis cannot be properly evaluated until many years have elapsed. Nevertheless observations of its effects both in primary syphilis and in neurosyphilis are sufficiently encouraging to justify its incorporation also into any program of therapy of cardiovascular syphilis. At the present time the recommended dosage is a total of between 5 million and 10 million units of penicillin administered intramuscularly in 30,000 to 40,000 unit doses every three hours for two to three weeks.[76, 55, 29a] It appears highly probable that this will be replaced by single daily injections of slowly absorbed crystalline procaine penicillin (600,000 units each) for fifteen to twenty days, thus permitting ambulatory treatment for most patients.

HERXHEIMER REACTIONS. Herxheimer reactions occur in about half of the penicillin treated cases but they develop with equal frequency whether the recommended doses or much smaller ones are given.[115, 32] Isolated instances of angina pectoris or heart failure following treatment have been reported,[26] but subsequent observations cast doubt on the relationship of the symptoms to the penicillin, except as a rare possibility.[92, 115, 30] Bismuth subsalicylate in doses of 0.1 gm. to 0.2 gm. intramuscularly at five-day intervals may be given prior to penicillin, with the hope that it may prevent or reduce the incidence of therapeutic shock.

Treatment of Uncomplicated Syphilitic Aortitis. The difficulty in recognizing such cases has been noted. It is probably present in a high percentage of individuals with latent syphilis, twenty to thirty years after the initial infection. Treatment may begin with intramuscular injections of penicillin, 600,000 units daily for ten days using either the single injection of penicillin-procaine or multiple injections of a watery solution every three hours. This is followed by bismuth subsalicylate 0.2 gm. intramuscularly once a week for twelve weeks. If there are no reactions and no appearance of angina pectoris, the bismuth should be followed by arsenoxide (mapharsen) beginning with 0.01 gm. intra-

venously once a week and increasing to a maximum of 0.03 gm. Courses of twelve injections of bismuth and ten of mapharsen are alternated for two years without a rest period. Potassium iodide 1.0 to 2.0 gm. three times daily may be continued throughout treatment of this and all other forms of cardiovascular syphilis.

All specific antiluetic treatment may properly be withheld in this group if the patient has had adequate treatment of his early syphilis and especially if he is past the age of fifty.

Treatment of Compensated Aortic Insufficiency or Asymptomatic Aneurysm. Treatment is similar to above but three injections of bismuth subsalicylate 0.1 gm. each at five-day intervals should precede initiation of penicillin therapy.

Treatment of Symptomatic or Very Large Aortic Aneurysms and Coronary Ostial Stenosis without Heart Failure. Following three injections of bismuth, the course of penicillin is given. Thereafter only bismuth is administered at weekly intervals for as long as two years if there is apparent improvement. If symptoms increase, bismuth is stopped. No arsenical drugs are given.

Heart Failure. In the presence of heart failure, no specific antisyphilitic therapy is administered. The heart failure is treated as described in Chapter 9. Digitalis is utilized as in other forms of congestive heart failure. If heart failure is thoroughly controlled, penicillin and intermittent courses of bismuth may be given cautiously with careful observation of the patient's response.

In the presence of concomitant neurosyphilis, penicillin is administered as above. The use of bismuth and arsenicals is determined by the status of the cardiovascular syphilis.

Symptomatic Treatment. Occasionally antisyphilitic treatment relieves such symptoms as nocturnal dyspnea or anginal pain. Angina pectoris should be treated symptomatically as described in Chapter 18. Paravertebral block may be required for relief. The same procedure occasionally relieves the pain of aortic aneurysm.[123] Often opiates are necessary.

Surgical Treatment. Although the surgical treatment of aortic aneurysms is generally discouraging,[88] there have been reports of successful results following the passage of a galvanic current through a coiled wire inserted into the aneurysmal sac.[37, 7] An aortectomy with excision of a thoracic aneurysm was successfully performed.[2] The use of a cellophane encasing of the aneurysm also appears promising in suitable cases.[84]

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THE HEART IN INFECTIONS

Rheumatic fever and syphilis are the only infections responsible for common clinical forms of cardiovascular disease. These have been discussed in previous chapters. Almost all of the microorganisms are capable at times of producing a bacterial endocarditis and less commonly a purulent pericarditis and myocardial lesions. The endocarditis and pericarditis are due to local implantation and growth of microorganisms, while the myocardial changes may be due either to the presence of these organisms or to toxic or metabolic disturbances caused by the infection.

This chapter is concerned with the cardiac abnormalities associated with a variety of more or less specific infections or infectious diseases, other than those mentioned above. Diphtheria is the classic example of an infection accompanied by sufficient anatomic change in the heart to account for clinical heart disease. In almost all of the other infections evidence of cardiac involvement consists either of electrocardiographic changes which are usually nonspecific and transient or of relatively mild and nonspecific myocardial lesions which are found in fatal cases.

Clinically, circulatory disturbances are uncommon or overshadowed by other manifestations of the infection. Acute circulatory failure (shock) is much more common than congestive heart failure. The latter is more apt to occur in patients with previous cardiac disease. Except for occasional instances of permanent heart block following diphtheria or of progressive heart failure due to myocardial involvement in schistosomiasis or sarcoidosis, chronic heart disease rarely results from any of the infections to be discussed. However, acute heart failure and unexpected deaths following certain infections have been attributed to myocardial involvement. During convalescence from many infectious diseases, dyspnea, precordial pain, extreme fatigability, symptoms resembling those of neurocirculatory asthenia, are not infrequent. It is improbable that they are due to myocardial disease.

THE HEART IN DIPHTHERIA

Incidence of Acute Myocarditis. Acute myocarditis is said to occur in 10 to 20 per cent of cases of diphtheria, the incidence being particularly high in epidemics with severe forms of the disease. Myocarditis may complicate cutaneous[20, 34] as well as faucial diphtheria and is often associated with cranial nerve involvement. Wesselhoeft[37] noted a mortality rate of 11.3 per cent in a series

of 15,490 cases of diphtheria; 59.4 per cent of these deaths were due to acute myocarditis.

Pathogenesis of Cardiovascular Disturbances. The circulatory disturbances in cases of diphtheria are due to the action of the exotoxin of the Klebs-Loeffler bacillus and not to the microorganism itself. The cardiac damage observed microscopically is likewise due to toxic effects on the muscle fibers, but the myocardial changes have been attributed also to toxic damage to the smallest coronary vessels with secondary myocardial anoxia.[16] The occurrence of shock in some cases of diphtheria is probably due to the effect of the toxin on the vasomotor activity of the peripheral vessels.

Pathology. Fahr[15] described three types of change in the heart: (1) fatty degeneration, (2) myolysis and (3) interstitial inflammation. Severe fatty, hyaline and other degenerative or necrotic changes in the muscle fibers occur near the end of the first and beginning of the second week.[21, 27, 12] Interstitial changes usually represent a secondary reaction to the parenchymal damage and appear in the latter half of the second week of the disease.[31] But interstitial myocarditis without parenchymal change has also been described.[26] The interstitial inflammatory alterations consist of edema and focal or diffuse infiltrations of lymphocytes, neutrophilic and eosinophilic leukocytes, monocytes and fibroblasts. The so-called toxic myolysis[14] denotes a solution of the muscle fibers; the sarcolemma is seen to surround a clear or hyaline substance without cross-striations or nuclei. Reparative changes, appearing during the second week, are represented by fibroblasts, granulation tissue, young collagen fibers and later by well formed scars. Scar formation is usually well established after three weeks.[17]

Clinical Features

Early Circulatory Disturbances. Acute circulatory failure may occur in the first few days. Electrocardiographic changes are usually absent. Tachycardia occurs commonly. Cough and cyanosis are usually due to respiratory obstruction by a diphtheritic membrane and not to myocardial failure.

Late (Convalescent) Cardiovascular Abnormalities. Near the end of the first and during the second week cardiovascular abnormalities may be due to an acute myocarditis. Occasionally severe cardiovascular symptoms appear four to seven weeks after the onset of diphtheria, particularly in cases of cutaneous diphtheria.[20] The clinical evidences of diphtheritic myocarditis are (1) electrocardiographic changes, (2) cardiac signs, (3) cardiac shock and more rarely (4) congestive heart failure.

Electrocardiographic Changes. Electrocardiographic abnormalities are usually the earliest evidence of acute myocarditis[25] and have been noted by Burkhardt et al.[9] in 20 per cent of 140 cases, by Altschuler et al.[2] in 24 per cent of 600 cases and even more frequently by other observers.[3, 6]

The earliest change is a mild saucer-shaped depression of the ST segment,[7, 33, 4] and by far the commonest change is a lowering or inversion of the T wave in two or more leads.[2]

Although conduction disturbances are much less frequent, they are more distinctive of diphtheritic myocarditis and denote a serious prognosis. Complete heart block has been considered characteristic, but prolongation of the P-R interval and more severe grades of partial heart block have been described.[23, 6, 24] Intraventricular conduction disturbances including bundle branch block

occur as commonly as complete heart block.[1, 13, 24] Since complete heart block in diphtheria may be associated with a normal or rapid ventricular rate, as well as with the more usual bradycardia, it may be overlooked on physical examination. As a rule the heart block persists less than a week. Complete heart block is usually ominous. All of the 11 patients with this disturbance in the series of Burkhardt et al.[9] succumbed; in Begg's[6] series, 8 of 12 patients with complete heart block died. Bundle branch block is similarly serious; there was a fatal outcome in 4 of 6 cases observed by Begg[6] and in all 4 of those recorded by Cookson.[13]

If the patient recovers, the electrocardiographic abnormalities including the severe conduction disturbances usually disappear rapidly. However, bundle branch block or complete heart block, said to have followed diphtheria, has been reported as still present after intervals between five and forty-two years.[29, 21, 5, 22]

Among other electrocardiographic changes recorded in cases of diphtheria are sinus tachycardia or bradycardia, transient extrasystoles and nodal rhythm, paroxysmal tachycardias with poor prognosis,[6] auricular fibrillation following complete heart block,[28] auricular flutter with varying grades of heart block,[5] prolongation of the Q-T interval[8] and postdiphtheritic ventricular fibrillation with recovery.[19]

Cardiac Signs. Tachycardia is usually present in the first week of diphtheria even when there is no myocardial involvement. With the development of acute myocarditis there is often a gradual or sharp reduction in the heart rate which may result in a mild or pronounced *bradycardia.* In the third week of the disease tachycardia may reappear in cases with myocarditis. Heart rates below 40 indicate the presence of complete heart block but the latter may be associated with a normal heart rate or a slight tachycardia. *Gallop rhythm* is an important sign of diphtheritic myocarditis with extensive myocardial damage and heart failure. Occasionally there is *cardiac enlargement.* Weakness of the first heart sound, tic-tac rhythm (embryocardia) and systolic murmurs have also been noted as evidence of myocarditis.

Cardiac Shock. Extensive myocardial damage may result in a sharp diminution in cardiac output and produce the clinical picture of shock. Usually this is preceded for several days by electrocardiographic changes and cardiac signs as described above. The clinical syndrome of cardiac shock usually appears in the second week of the disease and is sometimes heralded by striking pallor, vomiting and abdominal pain. A grayish cyanosis, coldness of the extremities, complete apathy, collapse of the peripheral veins and a sharp fall in blood pressure are prominent features. Tachycardia and a small, thready pulse are usual in shock but in the presence of complete heart block the pulse rate may be slow or relatively normal. Not infrequently the clinical picture of shock may result from peripheral circulatory failure rather than from cardiac damage.

Congestive Heart Failure. A moderate degree of congestive heart failure is usually associated with but overshadowed by the evidences of cardiac shock. The characteristic clinical picture of left- and right-sided failure, with signs and symptoms of pulmonary congestion and of peripheral edema and venous engorgement, occurs very uncommonly. This is probably due to the fact that either the patient succumbs from cardiac shock if the damage to the heart is sufficiently severe, or the myocardial changes regress if the patient survives. But I have seen a six year old boy who died with the typical clinical picture

of congestive heart failure three weeks after the onset of an attack of diphtheria which was undiagnosed and untreated until his admission to the hospital just before death. His electrocardiogram showed severe changes in the QRS complex including low voltage, notching, slurring, W shape in lead I, and a deep Q_4. The T waves were low and semi-inverted. The electrocardiographic appearance was that of a recent myocardial infarction.

Other Circulatory Abnormalities. Occasionally *intracardiac thrombi* are formed, especially in cases with subendocardial myocardial hemorrhage and inflammation which extend to the endocardium. These thrombi may be the source of emboli which produce isolated or repeated infarctions of the brain or lungs. Hemiplegia, cough and hemoptysis with pulmonary signs, and gangrene of an extremity have been observed.[11, 38]

Patients with complete heart block rarely suffer from epileptiform convulsions, syncope or other symptoms of the *Adams-Stokes syndrome*. Attacks of *angina pectoris* occur rarely. Late in the convalescent period, about the fourth to six week, patients may present a persistent tachycardia, or a tachycardia induced by slight effort or at the end of the day. A *bacterial (diphtheritic) endocarditis* due to the Klebs-Loeffler bacillus occurs rarely.

Diagnosis

The presence of acute myocarditis in a patient with diphtheria is indicated first by severe electrocardiographic abnormalities, especially complete heart block or bundle branch block. Clinically, a weakening or splitting of the first sound at the apex, gallop rhythm and cardiac enlargement usually denote an acute myocarditis. A severe myocarditis is revealed by the development of cardiac shock or congestive heart failure, usually in the second or third week of the disease.

Prognosis

Acute myocarditis is a serious complication of diphtheria, accounting for most of the deaths in this disease after the first week. According to Place[30] and others[18, 35] the mortality rate varies between 50 and 60 per cent, being almost 100 per cent in children between the ages of one and two, 50 per cent between two and ten, and 25 per cent among adults. In fatal cases death usually occurs in the first two weeks of the disease but occasionally later.

A poor prognosis is indicated by electrocardiographic evidence of heart block or bundle branch block and by certain clinical manifestations, such as a sudden drop in heart rate with resulting bradycardia, persistent and marked tachycardia in the second or third week of the disease, gallop rhythm, and especially the development of cardiac shock with or without congestive heart failure.

That diphtheritic myocarditis may lead to permanent fibrosis which predisposes to cardiac enlargement and congestive heart failure much later in life has been suggested but remains unproven.[32] On the other hand, certain conduction disturbances developing during the active myocarditis may persist for many months or years or even permanently (p. 836). Indirect evidence of permanent heart block due to diphtheria is presented by Butler and Levine.[10] In a group of 20 patients with proven heart block (14 complete, 6 partial) and without explicable cause such as coronary occlusion, syphilis or rheumatic fever, 50 per cent had had an attack of diphtheria in childhood. In a control

series of 600 consecutive surgical cases only 6 per cent had a history of diphtheria. If diphtheria leads to permanent heart block, this must be a rare development considering the frequency of diphtheria. Thompson, Golden and White[36] examined 100 persons who had had severe or moderately severe diphtheria from fifteen to twenty years previously; in none was there evidence of auriculoventricular or intraventricular block. They concluded that there is no proof that diphtheria contributes to the later development of heart block.

Treatment

The treatment of diphtheritic myocarditis is that of the underlying diphtheria. The early and adequate use of diphtheria antitoxin and penicillin is most important. Bed rest should be longer than in the uncomplicated case of diphtheria. Intravenous administration of 10 per cent dextrose solution, intramuscular injection of pitressin and subcutaneous injection of epinephrine are among the therapeutic measures used in cases of shock but with dubious merit. The routine widespread immunization of infants and children with diphtheria toxoid can almost eradicate diphtheria and its complicating myocarditis.

SCARLET FEVER

Confusion as to the occurrence of heart disease during scarlet fever has arisen from a failure to distinguish three forms of cardiac involvement:

1. Bacterial (hemolytic streptococcal) endocarditis, pericarditis or myocarditis.
2. Rheumatic heart disease (endo-, myo-, pericarditis).
3. Benign (nonbacterial) carditis due to scarlet fever per se.

Bacterial or Suppurative Cardiac Disease. Rarely there is an acute bacterial endocarditis or a suppurative pericarditis secondary to hemolytic streptococcal bacteremia. The latter arises from suppurative complications such as a purulent arthritis, osteomyelitis or more often a sinus thrombosis following otitis media and mastoiditis. In addition to endocarditis or pericarditis, there may be focuses of necrosis in the myocardium or abscesses of miliary or larger size. Embolic gangrene of an extremity associated with scarlet fever[44] is suggestive of a complicating acute streptococcal endocarditis.

Scarlet Fever and Rheumatic Heart Disease. This relationship was discussed above (p. 697) where it was concluded that scarlet fever, like other hemolytic streptococcal infections, could precipitate or reactivate rheumatic fever with subsequent rheumatic heart disease. When chronic cardiovalvular heart disease follows scarlet fever, the pathologic lesions are identical with those of rheumatic heart disease.[55, 51, 43, 47]

It is well known that scarlet fever may be followed shortly by arthritis which in turn may be complicated by endocarditis and chronic heart disease.[48] It is essential to distinguish two forms of nonsuppurative arthritis associated with scarlet fever. First, there is a true scarlatinal synovitis or arthritis, such as occurs with other infections, which is unrelated to rheumatic fever and is never followed by heart disease.[41] Second, there may appear a true rheumatic polyarthritis, usually in subjects with preexisting rheumatic heart disease, in whom rheumatic infection is reactivated by the scarlet fever. In general, benign scarlatinal arthritis occurs earlier, usually between the fourth and tenth days of the disease; rheumatic arthritis usually appears in the third or fourth

week of the disease. The benign arthritis, like other forms of infectious arthritis, frequently involves the joints of the fingers and hands, while these joints are uncommonly affected in rheumatic fever.

Scarlatinal (Benign) Carditis

This refers to nonspecific electrocardiographic, clinical and pathologic changes, similar to those observed in many other infectious diseases. Such cardiac complications were noted in 106 (6 per cent) of 1770 cases studied by Rosenbaum.[53] A definite verrucous endocarditis with permanent valvular damage has been reported rarely,[60, 58] but the rheumatic or bacterial origin of the verrucae must be considered. Similarly, occasional instances of pericarditis attributed directly to scarlet fever were probably due to an activation of rheumatic fever or to a complicating streptococcal bacteremia. Scarlet fever does not appear to produce a chronic form of heart disease independent of rheumatic or bacterial (suppurative) complications.

Pathology. As a rule there are no significant myocardial lesions or only mild degenerative changes such as cloudy swelling of the muscle fibers. Occasionally there are mild focal or diffuse interstitial cellular infiltrations of lymphocytes and plasma cells, and less often of neutrophilic or eosinophilic leukocytes. But some observers have claimed that the myocardial lesions of scarlet fever are more severe and occur frequently.[42, 57, 50] Great care is necessary not to misinterpret the myocardial lesions of diphtheria, for the latter disease may occur coincidentally in about one fifth of the cases of scarlet fever and may be unrecognized clinically.

Clinical Features. The so-called scarlet fever heart has been diagnosed near the end of the first week of the disease, or during convalescence,[54] on the basis of (a) a weak, muffled or split first sound, (b) a systolic murmur with an alleged characteristic quality, sometimes resembling a pericardial rub, (c) occasional accentuation or reduplication of the second pulmonic sound, (d) cardiac enlargement. It is doubtful whether a distinctive scarlet fever carditis can be demonstrated by physical examination.

Electrocardiographic Changes. Mild, nonspecific electrocardiographic abnormalities occur in 5 to 10 per cent of cases of scarlet fever.[56, 45, 46] The most frequent changes according to Shookhoff and Taran[56] are minor ST segment deviations and lowering or inversion of the T waves, but according to others, a prolongation of the P-R interval is more common. The possibility of a complicating rheumatic fever should be investigated when conduction disturbances are encountered two or three weeks after the onset of scarlet fever. Occasionally more severe grades of partial heart block have been observed,[39, 49, 59] including rare instances of transient complete heart block with or without Adams-Stokes syndrome.[49, 40, 52] Nodal rhythm and nodal extrasystoles, and auricular flutter have also been recorded.

ACUTE TONSILLITIS AND NASOPHARYNGITIS

Clinical, electrocardiographic or pathologic evidence of myocarditis following acute tonsillitis or nasopharyngitis has been reported by several observers.[63, 61, 62] Gore and Saphir[62] studied 35 cases in which the pathologist found evidence of myocarditis and death from cardiac failure, but heart disease had been suspected clinically in only three of these. In 15 cases death occurred unexpectedly.

PNEUMONIA

A bacterial (pneumococcic) endocarditis occurs in about 4 per cent of cases of lobar pneumonia,[87] usually in association with meningitis (p. 809). The pneumococcus also causes occasionally a fibrinous, serofibrinous or suppurative pericarditis, usually by direct extension from a pleuritis or empyema. Myocardial lesions may occur in both pneumococcic endocarditis and pericarditis.[84] In addition, nonspecific myocardial lesions may be associated with a pneumococcus pneumonia without local bacterial involvement of the heart.

Pathology. Most observers have reported only insignificant degenerative parenchymatous changes of the heart muscle or occasional mild interstitial inflammatory lesions.[66, 85, 86] However Saphir and Amromin,[82] in a study of the hearts of 67 patients with bronchopneumonia involving at least the total of one whole lobe, found significant inflammatory changes in 26 or 38.8 per cent. There were interstitial and often perivascular accumulations of neutrophilic polymorphonuclear leukocytes, lymphocytes and endothelial leukocytes.

Pathologic Physiology. The myocardial lesions are rarely, if ever, sufficient to cause serious dysfunction of the normal heart. However, severe cases of pneumonia may be complicated by acute circulatory failure (shock), probably due to the toxic effects of the pneumococcus and its products on the capillary system.[81, 71]

Pneumococcus pneumonia may impose serious cardiac strain on a heart which is the site of preexisting organic disease. Evidence of such preexisting heart disease was found by Brooks[65] in 116 of 200 autopsied cases of lobar pneumonia. Congestive heart failure may be precipitated by the strain of fever, infection, toxemia and cough, by increased resistance in the pulmonary circulation due to pulmonary consolidation,[72] and by disturbances in the excretion of sodium and water associated with pneumonia.

Electrocardiographic Changes. Transitory electrocardiographic changes during the course of lobar pneumonia were observed in 42 of 45 patients by Master et al.,[78] in 25 per cent of 975 cases by De Graff et al.[68] and in 43 per cent of 82 cases by Thomson and associates.[86] The common abnormalities are flat, low-voltage or inverted T waves in leads I and II and in precordial leads.[77, 64, 86] Alterations in the ST segment were described by Master et al.[78] but not by other observers. A slight prolongation of the P-R interval was observed in 9 per cent of the cases described by De Graff et al.[68] but not in those of Thomson et al.[86] Occasionally there is slurring and widening of the QRS complexes or bundle branch block.

Tachycardia is usual before the crisis, and a bradycardia, often associated with sinus arrhythmia, is common during convalescence. Auricular flutter or fibrillation occurs occasionally, as a rule in elderly patients and those with underlying heart disease. The electrocardiographic changes occur chiefly after defervescence, but also before and during the crisis.

Size of the Heart. The size of the heart was studied by Levy[76] by means of successive roentgenograms during the course of the disease. He reported a significant enlargement in 61.9 per cent of 21 cases. It is often difficult to exclude the factor of abdominal distention with elevation of the diaphragm in modifying the position and apparent size of the cardiac silhouette. Associated cardiac failure and sodium-water retention in the course of lobar pneumonia may account for definite enlargement of the heart in some cases.

Circulatory Measurements. The *blood pressure* remains fairly constant but usually falls sharply if acute circulatory failure develops.[81, 71]

The *venous pressure* is usually normal but may be elevated, especially in persons with preexistent heart disease and congestive heart failure.[73, 74]

The *circulation time* is usually normal but was prolonged in about 10 per cent of 75 cases studied by Hitzig et al.[73] and in about 25 per cent of those observed by Sigler et al.[83] The prolonged circulation times were encountered more often in those who succumbed than in those who recovered, and in those beyond the age of forty-five than in those below that age.

The *circulating blood volume* was found to be normal in cases without circulatory failure.[73]

The *cardiac output* was found to be increased during the febrile stage, below normal after the crisis, and back to normal only after one to three weeks.[75]

Congestive Heart Failure and Acute Circulatory Failure. Acute circulatory failure (shock) occurs most often in very toxic cases of lobar pneumonia, especially those associated with bacteremia and consolidation of multiple lobes. It usually occurs at the height of the disease just before the crisis, occasionally earlier and less frequently after the crisis. The clinical picture is that of apathy or restlessness and disorientation, weak, rapid pulse, cold extremities, grayish cyanosis, collapsed peripheral veins and a terminal drop in blood pressure in fatal cases. Although the occurrence of shock in pneumonia is of ominous significance, recovery is not rare.

Congestive heart failure is less common than shock; it usually occurs only in elderly patients and those with preexistent organic heart disease.[65] Left-sided heart failure is difficult to recognize in the presence of pneumonia, but the diagnosis may be aided by finding a prolonged circulation time. Pulmonary edema may occur in severe and fatal cases of pneumonia, due to toxic damage and increased permeability of the pulmonary capillaries. In such instances of pulmonary edema not due to left heart failure, the circulation time is normal.[73] Right-sided heart failure is revealed by venous congestion, increased venous pressure and moderate hepatic enlargement, but peripheral edema is usually absent or occult.

Treatment of Circulatory Complications. The most important measures are the early and adequate use of chemotherapy and antibiotics to control the underlying infection. Theoretical considerations and clinical results[79, 67] suggest that digitalis should not be administered in uncomplicated cases of lobar pneumonia. However, it should be given if there is definite evidence of congestive heart failure with or without auricular fibrillation.

Atypical Pneumonia. In a series of 321 cases of atypical pneumonia 3.7 per cent revealed changes in the RST segments, flattening or inversion of T waves and prolongation of the P-R interval or of the QRS complex in the electrocardiogram.[80] The changes have been interpreted as evidence of myocardial involvement; in some instances they are identical with those described under acute pericarditis.[70, 69]

INFLUENZA

The influenza bacillus causes about 3 to 5 per cent of the cases of *bacterial endocarditis*.[95] Rarely it may produce a fibrinous or purulent *pericarditis*.

Myocardial changes are uncommon and mild. They consist of cloudy swelling of the muscle fibers and focal or diffuse collections of round cells and

histiocytes.[94] Rarely there are more severe destructive changes of muscle fibers.[98]

Cardiovascular disturbances are uncommon. Acute circulatory failure may occur in toxic cases and rarely congestive heart failure.[91] During convalescence weakness, precordial pain, palpitation and dyspnea are common.

Electrocardiographic Changes. A prolongation of the P-R interval is not uncommon and occasionally there is more severe partial heart block.[92, 90, 99, 96] Complete heart block has also been reported.[97] This may be associated with Adams-Stokes syndrome and may disappear after a few days.[89]

Sinus bradycardia is common during convalescence. Extrasystoles, sinoauricular block, wandering pacemaker, nodal rhythm, tall notched P waves and abnormalities of the T wave and S-T interval have also been observed occasionally.[93] Occasional death from acute coronary thrombosis has been noted in young adults following an attack of influenza.[92, 88]

TYPHOID FEVER

A bacterial endocarditis or pericarditis due to Eberth's bacillus is extremely rare. Myocardial lesions are infrequent, mild and nonspecific.

Pathology of the Myocardium. According to older observers, such as Romberg,[108] typhoid fever was said to be associated frequently with severe parenchymatous and interstitial myocarditis. But more recent studies have disclosed merely cloudy swelling of the muscle fibers, a mild degenerative change seen in many infections. Very infrequently there is an interstitial myocarditis with an infiltration of round cells and polymorphonuclear leukocytes. Arteritis and thrombosis of the coronary vessels have been described as a rare occurrence.[104]

Electrocardiographic Abnormalities. Electrocardiographic abnormalities occur in the majority of cases of typhoid fever either during the acute illness or during convalescence. [100, 102, 106, 105, 107] The commonest changes are *flat, diphasic or inverted T waves* in two or more leads. These abnormalities usually appear in the third or fourth week of the illness and return to normal one to three weeks after the onset of convalescence. In 23 of 35 patients with T wave abnormalities, Rachmilewitz and Braun[107] observed a rapid normalization of the electrocardiogram following the administration of niacin.

A prolongation of the P-R interval has been noted by some observers, especially during convalescence, but this was found only once in Mainzer's[105] series of 106 cases. Occasionally complete heart block has been recorded.[101, 103]

Relative bradycardia is characteristic of the febrile stage. True bradycardia and sinus arrhythmia are common during convalescence, but tachycardia may appear in the third to fifth week of the illness, as an evidence of myocarditis, effort syndrome or of complications such as intestinal hemorrhage or perforation.

Clinical Circulatory Disturbances. Acute circulatory failure (shock) occurs occasionally as a result of toxemia, dehydration or hemorrhage. I have seen a boy, aged fifteen, admitted on the fifth day of his illness, with evidence of extreme dehydration and shock. The heart rate was 140, the pulse thready, the heart sounds weak and tic-tac in quality. The blood pressure was too low to measure accurately. He recovered after transfusions.

Congestive heart failure is extremely rare except in cases of preexisting heart disease. In a woman of twenty-five whom I observed, tachycardia, gallop rhythm, cardiac enlargement, and hepatomegaly were noted five weeks after

the onset of typhoid fever. The electrocardiogram revealed inversion of the T wave in leads I, II and IV. These changes disappeared only after three months, while the cardiac abnormalities did not disappear until four months after they were first noted.

MENINGOCOCCUS INFECTIONS

The meningococcus may produce an *acute or subacute bacterial endocarditis* (Chapter 34) with or without meningitis.

Pericarditis also may result from a meningococcemia and is usually associated with meningitis. But in the case reported by Orgain and Poston,[113] meningococcus pericarditis with a large effusion and tamponade of the heart occurred without a history of preceding meningococcemia or meningitis. Herrick[112] observed pericarditis 12 times among 280 cases of meningococcus meningitis; 6 were fibrinous and 6 were associated with purulent or seropurulent effusions of 30 to 640 cc. Conklin[109] reported a case in which there was a turbid effusion of 1500 cc. Recovery may occur spontaneously or with the aid of pericardial paracentesis, sulfonamides and penicillin.

Myocarditis was observed post mortem in 111 of 256 cases of meningococcemia.[110] There are microscopic foci of interstitial and perivascular cellular infiltrations. Occasionally there are microscopic or macroscopic abscesses with destruction of muscle fibers.[111, 114, 115] Intracellular and extracellular gram-negative diplococci have been demonstrated.

Isolated electrocardiographic changes have been noted. In one case of prolonged meningococcemia without meningitis which I observed, there was a transient prolongation of the P-R interval to 0.24 second. Distinct R-T elevations should suggest the presence of pericarditis.

UNDULANT FEVER

Infections with brucella organisms rarely involve the heart, a *bacterial endocarditis* being the most frequent cardiac complication.[122] This occurred in 1 per cent of 300 cases studied by Hardy.[119]

Pericarditis with effusion also occurs rarely and was noted twice by Hughes[120] and once in association with endocarditis by Hardy.[119]

The myocardium may disclose an infiltration of small and large round cells, and moderate cloudy swelling and granular degeneration of the myocardial fibers.[117]

Electrocardiographic abnormalities found by Rubegni[121] included elevations or depressions of the RS-T interval and low, isoelectric or inverted T waves. Usually the electrocardiographic changes revert rapidly to normal, but I have seen inverted T waves persist for two months. Auricular fibrillation has been noted.[116] Acute circulatory failure occurs occasionally.[118]

TUBERCULOSIS

Tuberculosis may be associated with extensive pulmonary changes causing increased pulmonary vascular resistance, pulmonary hypertension and chronic cor pulmonale (Chapter 39).

Tuberculosis may involve the heart directly, most often causing a tuberculous pericarditis with effusion (p. 517) with or without compression of the heart (Chapter 23).

Tuberculosis of the myocardium is rare although more than 200 cases have

been reported.[130] Custer and Charr[125] discovered an incidence of 0.44 per cent in about 15,000 cases of tuberculosis. The myocardium is most often involved by an extension of contiguous pericardial lesions but occasionally by infection from the blood stream. Three types of lesions have been described: the miliary, the large nodular and the diffusely infiltrating.[128] The latter may cause widespread destruction as in the case of Bellet et al.,[124] in which it extended from the pericardium through the ventricular myocardium to reach the endocardium. The large nodular or the infiltrating lesions may rupture into the cardiac cavity and cause a disseminated tuberculosis. The infiltrating type may involve the atria and cause auricular fibrillation. The large nodular lesions are usually found in the atria and may form tumor-like nodules termed tuberculoma.[131] They may be asymptomatic or cause obstruction to blood flow.

Myocardial tuberculosis is usually asymptomatic. Involvement of the atria may result occasionally in auricular premature beats, auricular flutter or fibrillation.[133] These arrhythmias in a patient with tuberculosis, especially tuberculous pericarditis, should suggest atrial involvement.[127] Paroxysmal ventricular tachycardia has been recorded as occurring with myocardial tuberculosis.[132] Congestive heart failure was attributed to extensive myocardial scarring secondary to tuberculous myocarditis in one of Wilbur's[134] cases.

Endocardial tuberculosis is the rarest form of cardiac tuberculosis. The endocardium may be involved by extension of pericardial or myocardial lesions or as part of a disseminated miliary tuberculosis. Rarely isolated tuberculous valvular endocarditis has been reported.[123, 126, 129]

SARCOIDOSIS

Sarcoidosis is probably an infection, resembling noncaseating tuberculosis, but associated with a negative tuberculin reaction. It may affect the heart by direct myocardial involvement or by causing right heart strain secondary to extensive pulmonary involvement (p. 900).

Sarcoidosis produces yellowish circumscribed or diffuse tumor-like infiltrations of the heart, which consist of granulomata containing very large giant cells as well as epithelioid and plasma cells and lymphocytes, but no polymorphonuclear leukocytes. Myocardial damage may be caused by the active granulomata or by subsequent scarring and replacement of muscle fibers.

Sarcoidosis of the myocardium may be asymptomatic, but congestive heart failure is not unusual.[137] In 6 of a series of 31 patients studied by Longcope and Fisher,[139] there was evidence of myocardial insufficiency during life or sarcoidosis of the heart was discovered at autopsy. In 5 of the cases with heart failure there were also enlargement of the heart, arrhythmia and electrocardiographic changes. In the cases reported by Bates and Walsh[135] there was extensive myocardial sarcoidosis, but tachycardia was the only clinical symptom.

Electrocardiographic abnormalities[140, 136, 139, 138] consist of prolonged P-R interval, bundle branch block, prolonged QRS, ST segment depressions, flat or inverted T waves and occasional prominent P waves.

ACTINOMYCOSIS

Actinomycosis rarely affects the heart. As a rule the pericardium is affected by extension of neighboring lesions in the lungs, mediastinum or other thoracic structures.[143] Very rarely the myocardium is invaded by way of the general blood stream or coronary arteries and occasionally by extension of pericardial

actinomycosis. Bacterial endocarditis due to Actinomyces bovis has been reported, the valvular lesion being the only lesion in the heart.

The pericardium reveals necrotizing, suppurative and sclerotic lesions.[141] There is usually a seropurulent, yellowish cloudy fluid which is occasionally hemorrhagic. The pericardial layers become thickened and adherent. The fibrocaseous material extends to the myocardium and even to the endocardium, producing necrosis and abscesses and masses of various sizes. These masses may obstruct a valvular orifice,[142] or may break into the cardiac cavities or coronary veins and cause a dissemination of actinomycosis.

Despite amazingly extensive lesions, there may be no clinical symptoms referable to the heart. As a rule, the cardiac symptoms when present are overshadowed by those referable to the primary disease. Involvement of the heart may be suspected in a patient with actinomycosis if there are evidences of pericarditis, arrhythmias or congestive heart failure. In Uhr's[144] case the entire clinical picture of bacterial endocarditis was due to the valvular lesion.

VIRUS INFECTIONS

Infectious Hepatitis. Electrocardiographic changes consisting of T wave depressions were found in 9 of 11 cases studied by Dehn et al.[145]

Infectious Mononucleosis. The electrocardiogram disclosed low voltage of the QRS and T waves in 4 of 100 cases and in 2 of these the T wave was inverted.[146] In one patient there was a pericardial rub and in another a pericardial effusion.

Influenza A. Two cases of nonbacterial myocarditis, in one of which death resulted from heart failure, were recorded by Finland et al.[148]

Epidemic Parotitis (Mumps). T wave changes and a prolongation of the P-R interval were described by Wendkos and Noll.[153] Rosenberg[151] observed electrocardiographic abnormalities in 15 per cent of 104 cases, usually during the fifth to tenth day of the illness. There were inversion of T waves, elevation of the ST in CF_4, biphasic or inverted P waves, prolongation of the P-R interval and 1 case each of partial and complete heart block. In a case reported by Felknor and Pullen[147] there was clinical evidence of congestive heart failure including gallop rhythm, tachycardia, enlargement of the liver and râles at the bases of the lungs.

Acute Anterior Poliomyelitis. Electrocardiographic changes were found in 14 per cent of 467 patients.[149] They occur early and may persist several weeks. Prolongation of the P-R interval and flat or inverted T waves are the abnormalities encountered. Pathologically microscopic perivascular and interstitial cellular infiltration and edema are occasionally observed.[152, 150]

RICKETTSIAL DISEASES

Typhus Fever. Gore and Saphir[154] found pathologic evidence of myocarditis in 23 of 48 fatal cases of epidemic typhus and in 9 of 19 cases of Rocky Mountain spotted fever. Herzog and Rodriguez[155] described: (1) vascular changes, (2) perivascular and subendocardial interstitial nodules and (3) diffuse interstitial inflammatory changes in 97 per cent of 103 hearts in an epidemic of typhus fever in Chile. Capillary and precapillary vessels undergo endothelial proliferation, occasional necrosis, inflammation of the vessel wall, occasional mural thrombosis and a pericapillaritis.

Acute circulatory failure (shock) may occur in the middle of the second week

or earlier in toxic cases.[158] Gallop rhythm is occasionally heard but frank congestive heart failure is rare.

Electrocardiogram. Low, isoelectric, diphasic or inverted T waves were observed in 72 per cent of 85 cases and a prolongation of the P-R interval in 48 per cent.[158] In one case there was a right bundle branch block and at postmortem examination the heart presented multiple small infarcts due to necrotizing thromboarteritis of the small vessels. In patients recovering from typhus fever the electrocardiographic abnormalities disappear and there is no chronic heart disease.

Scrub Typhus (Tsutsugamushi Fever). Pathologic evidence of myocarditis was found by Gore and Saphir[154] in all of 227 cases of scrub typhus. Endothelial proliferation and perivascular infiltrations of round cells and necrosis of muscle fibers are the commonest findings.[157] Minor electrocardiographic abnormalities include ST segment depression or elevation and low T waves.[159, 156] In 5 or 6 patients with cardiac decompensation Hollander[156] found low amplitude of the QRS complexes.

TRICHINOSIS

Trichinosis is not infrequently associated with pathologic and electrocardiographic evidence of myocarditis.[163, 167]

Pathology. There are interstitial and perivascular collections of eosinophilic and neutrophilic leukocytes, lymphocytes and occasional mononuclear and plasma cells, associated with focal necrosis of the muscle fibers.

The Trichinella spiralis was observed in the myocardium in the case of Zenker,[169] and in one of Terry and Work.[168] In Spink's[167] case the larvae were found after digestion of the heart muscle with artificial gastric juice, although not demonstrable on histologic examination. As a rule, however, the larvae are not observed in the heart. It is believed, on experimental grounds, that the myocardial changes are caused by the presence of the trichinella larvae, but that they do not become encysted in the heart and either die early or migrate elsewhere.[162, 164] Therefore they are not observed if death occurs after the first week or two.

Clinical evidence of myocarditis is usually absent. Occasionally there is acute circulatory failure (shock). I have twice noted gallop rhythm. In these two cases there were other evidences of congestive heart failure, including dyspnea, venous engorgement and peripheral edema. Terry and Work[168] reported a verified case of trichinosis myocarditis which was mistaken for rheumatic fever because of the combination of arthritis, fever, epistaxis and a prolonged P-R interval in the electrocardiogram.

Electrocardiographic changes were observed in 2 of 44 cases of Beecher and Amidon,[160] in 6 of 18 by Spink,[167] in one third of the cases studied by Cushing,[161] and in 21 per cent of 114 cases observed by Solarz.[166] Flattening or inversion of the T waves occurs in two or more limb leads, especially lead II or leads I and II, and in the precordial leads. Occasionally upward convexity of the RS-T segment and cove-plane type of T inversion simulate the changes seen in acute myocardial infarction.[161, 165] A prolongation of the P-R interval, low voltage of the QRS and intraventricular block are noted occasionally. The electrocardiographic changes appear in the second week of the disease and disappear within a month or two, but a prolongation of the QRS may persist.[166]

ECHINOCOCCUS INFECTIONS

Cardiac involvement by echinococcus (hydatid) cysts occurs rarely, and in about 0.5 to 1 per cent of all echinococcus disease. Dévé[171] analyzed 137 cases of cardiac echinococcus disease, in 83 per cent of which the primary echinococcus infestation was limited to the heart, while in the remainder the cardiac cyst coexisted with one or more primary cysts in other organs, particularly the liver. Any chamber of the heart may be involved with cysts, which vary in size from that of a cherry to that of an orange. A review of echinococcus cyst of the left side of the heart was presented recently by Peters and associates.[175]

In the absence of complications there are no symptoms, the cysts being found accidentally at postmortem examination. Some patients suffer from palpitation, arrhythmias, attacks of dyspnea or precordial oppression. Local effects of large cardiac cysts include peculiar murmurs, enlargement of the cardiac silhouette or bizarre shadows in the cardiac contours on roentgenologic examination. Involvement of the interventricular septum has caused intermittent heart block with Adams-Stokes syndrome.[172]

Single or recurrent rupture of a cyst into the cardiac cavity may cause (a) sudden death from anaphylactic shock or obstruction of a valvular orifice, (b) anaphylactoid reactions with anxiety, vomiting and shock, (c) embolism of cysts with obstruction of the vessels to the brain, lungs, abdominal viscera or extremities.[176] Recovery may be complicated by hemiplegia, gangrene or renal shut-down. Rupture of the cysts into the pericardium occurs occasionally with inflammatory reaction and adherent pericardium.

Diagnosis may be suggested by the combination of (a) echinococcus cyst elsewhere, blood eosinophilia and positive skin or serologic tests for echinococcus, together with (b) suggestive roentgen ray evidence of calcified cysts in the heart, bizarre shadows in the cardiac silhouette, peculiar cardiac murmurs or a sudden anaphylactic shock-like syndrome with or without embolization. Diagnosis is important because of the possibility of surgical treatment. An echinococcus embolism of the axillary artery was removed by Köhler.[173] In several cases cardiac echinococcus disease was diagnosed during life.[170] In one case the diagnosis was made roentgenographically and treated successfully by operation.[174]

TRYPANOSOMIASIS (CHAGAS' DISEASE)

This is a common South American disease caused by the Trypanosoma cruzi and transmitted by a bedbug vector, the Panstrongylus magistus.[177] It occurs as an acute generalized disease in which the myocardium is almost always involved, and as a chronic disease with predominant cardiac manifestations.[178] In the acute form there are diffuse myocardial lesions with extensive destruction of muscle fibers associated with a mononuclear interstitial myocarditis. In the chronic form there is a predominant interstitial myocarditis with infiltration of lymphocytes, plasma cells, mononuclears and macrophages, and diffuse fibrosis. All parts of the heart are involved.

The acute form of the disease is dominated by generalized evidences of toxemia and disseminated lesions, but sudden death may result from cardiac involvement. The chronic form is characterized by insidious onset, profound weakness, palpitation and precordial pain, dyspnea on effort, cardiac enlarge-

ment, and all the objective evidences of progressive congestive heart failure. The clinical picture may simulate coronary artery disease.[181] Syncope occurs commonly and may be due to complete heart block. Sudden death occurs frequently. A special characteristic of the disease is the frequency of all forms of arrhythmias and conduction disturbances.[179] These include marked bradycardia, partial and complete heart block, premature contractions, auricular flutter and fibrillation, and right bundle branch block.[180] The QRS complexes are of low voltage.

CARDIAC DISEASE DUE TO OTHER INFECTIONS, INTOXICATIONS, DRUGS OR PHYSICAL AGENTS

Electrocardiographic or pathologic evidence of myocardial involvement has been described in a variety of other infections, among them focal infections,[197, 193] bronchiectasis and a number of bacterial infections besides those specifically discussed. Electrocardiographic changes and evidence of myocardial, pericardial and endocardial involvement have been reported in Reiter's disease.[196, 191] Myocarditis has also been noted occasionally in infections with other higher bacteria, yeasts or fungi such as coccidioidomycosis, blastomycosis, torulosis, toxoplasmosis,[192] histoplasmosis[191a] and sarcosporidia.[181a]

Myocardial lesions have been attributed to the metabolic toxins associated with uremia (p. 866) and those associated with extensive burns,[183] serum sickness,[185] and cutaneous lesions.[182] Recently considerable interest has been aroused by the finding of severe interstitial myocarditis following the experimental or clinical administration of sulfonamides.[189, 194, 188]

Phosphorus poisoning may produce intense fatty degeneration of the heart and electrocardiographic abnormalities[187] but the clinical picture is dominated by concomitant hepatic damage. *Carbon monoxide poisoning* will be discussed (p. 975). Cardiac abnormalities due to overdosage with digitalis (p. 190) and quinidine (p. 281) have also been discussed. Myocardial necrosis and calcification have been observed following poisoning with bichloride of *mercury*. Acute interstitial myocarditis has been described in a case of exfoliative dermatitis following arsphenamine administration.[184] *Emetine* causes inversion of the T waves in two or more leads, occasional changes in the QRS complex, dyspnea, tachycardia, apical systolic murmurs and even gallop rhythm.[186]

Myocardial lesions have also been noted following deep roentgen ray therapy to organs adjacent to the heart.[190, 195]

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37

THE HEART IN HYPERTENSION AND RENAL DISEASE

THE HEART IN HYPERTENSION

Hypertension and Hypertensive Heart Disease

Hypertensive heart disease is generally regarded as the commonest form of cardiac affection. Nevertheless the exact kinship between hypertension and heart disease is obscure, and the delineation of hypertensive heart disease as a pure etiologic entity, independent of other forms of heart disease, is ill defined.

The causal relationship of hypertension to heart disease is based, first of all, on the frequency with which the two conditions are associated.[31] In a series of over 30,000 autopsies with 4700 cardiovascular deaths, about 45 per cent of the latter were due to hypertensive heart disease.[24] The course of hypertension also supports its relationship to heart disease, for at least 60 to 75 per cent of hypertensive patients ultimately succumb from cardiac complications, especially heart failure.[12, 31, 47, 70, 97] Finally it is believed that the physiologic disturbances associated with hypertension are such as to impose a serious strain on the heart (p. 858). In summary, the concept of a form of heart disease due to hypertension, per se, is based on (1) the very high incidence of hypertension in cases of heart disease, (2) the predominant frequency of ultimate cardiac disease in hypertensive patients, and (3) physiologic evidence that hypertension increases the work and otherwise strains or impairs cardiac function.

Hypertensive and Arteriosclerotic (Coronary) Heart Disease. The exact causal relationship between hypertension and heart disease is obscured by two types of data:

(1) There is a lack of correlation in most cases between the severity and duration of hypertension and the development of cardiac complications.

(2) Hypertension is associated with a high incidence of coronary arteriosclerosis. On the one hand Clawson,[23] in a necropsy study of about 1000 cases of arteriosclerotic (coronary) heart disease, found that hypertension had been present in about 70 per cent. Conversely coronary sclerosis has been found in 90 per cent of hearts of persons dying with hypertension.[31] The relative importance of coronary arteriosclerosis and hypertension in producing clinical heart disease is suggested by the clinicopathologic observations of Averbuck.[6] In two similar groups of hypertensive cases which came to autopsy, significant

coronary sclerosis was found in 85 per cent of those with clinical heart disease and in only 10 per cent of those without heart disease.

Careful clinical and pathologic study of the problem over many years has impressed me with the predominant importance of coronary arteriosclerosis in determining the manifestations of so-called hypertensive heart disease. The frequency of severe coronary arteriosclerosis is still underestimated at post-mortem examinations unless the entire coronary tree is systematically investigated, preferably with special technics. This concept of the importance of coronary arteriosclerosis in determining the clinical course of hypertensive heart disease does not exclude any causal relationship between hypertension and the coronary arteriosclerosis or the possibility of some common mechanism. Nor does it exclude the mechanical or other effects of hypertension on the heart which increase its susceptibility to injury by means of a deficient coronary blood supply.

Occasionally, and particularly in the experience of coroners, sudden death in hypertensive individuals is associated with pronounced cardiac hypertrophy and heart weight exceeding 400 gm., without significant coronary disease. In such cases the cardiac disease and sudden death are attributed exclusively to hypertension, in the absence of any other discoverable cause. In cases of malignant hypertension heart failure develops frequently in the last stages while coronary arteriosclerosis is usually not severe. The heart failure may be attributed to the strain of the hypertension and the consequent pronounced cardiac hypertrophy, but renal impairment in the excretion of sodium and water may also be an important causative factor.

Etiology of Hypertensive Heart Disease

The etiology of hypertensive heart disease is obscured by uncertainty as to the genesis of the underlying hypertension. A detailed discussion of hypertension, per se, is beyond the scope of this book. Only a brief résumé is given in order to obtain a better orientation towards its relationship to hypertensive heart disease.

There is no universal agreement as to the dividing line between normal and high blood pressure. In this discussion, hypertension refers to a persistent elevation of the diastolic blood pressure above 90 mm. Hg. As a rule, the systolic blood pressure is also elevated above 140 mm. Hg. Systolic hypertension may occur without elevation of the diastolic pressure, but it is much less important or insignificant in the development of clinical heart disease.

Essential Hypertension and Secondary Hypertension. Hypertension is associated with or due to a variety of conditions, notably:

(1) Renal diseases (acute and chronic glomerulonephritis, chronic pyelonephritis, polycystic kidneys, renal tumors, periarteritis nodosa, renal vascular-anomalies and occlusions, toxic nephroses);

(2) Endocrine diseases (Cushing's syndrome; pheochromocytoma);

(3) Vascular disease (coarctation of the aorta);

(4) Cerebral lesions (brain tumor; bulbar poliomyelitis).

Hypertension associated with these primary diseases is sometimes termed secondary hypertension. In the largest group of hypertensive cases, no apparent underlying disease can be discovered. These are therefore termed "primary" or essential hypertension.

Theories of Hypertension. *Endocrine Theory.* Tumors of the adrenal medulla

(p. 945) cause paroxysmal and occasionally persistent hypertension, but this is dissimilar to essential hypertension. More significant is the hypertension associated with hyperfunction of the adrenal cortex as exemplified by basophilic pituitary tumors and adrenal cortical tumors (Cushing's syndrome) (p. 944). Conversely, there is pronounced hypotension in Addison's disease in which there is a deficiency of the adrenal cortex. In cases of Addison's disease the continued administration of the synthetic adrenal cortical hormone, desoxycorticosterone (DCA), together with sodium chloride may produce hypertension[83] (p. 947). The same procedure in hypertensive patients leads to further elevation of the blood pressure.[80, 82] DCA has also been found to have an immediate pressor effect when injected intravenously in hypertensive individuals.[45] In animals, the adrenals appear to be necessary to the production or maintenance of experimental hypertension by renal ischemia,[72] and DCA has been reported to produce hypertension and arteriosclerosis in rats.[98]

These observations may indicate merely that the endocrine glands are responsible for one small group of cases of hypertension, or that the adrenal cortex in particular may be one element in a complex cycle of events leading to human hypertension. Concepts attributing to the adrenal cortex and/or to the pituitary-hypothalamic centers a major role in hypertension have been formulated by Selye[99] and by Heinbecker.[54]

Renal Genesis of Hypertension. 1. ASSOCIATION WITH INTRINSIC PRIMARY RENAL DISEASE. The association of hypertension with a variety of intrinsic diseases of the kidney has long been known. In these cases the bilateral renal disease precedes the hypertension and is generally regarded as the cause of the hypertension, but the mechanism is uncertain.

2. EXPERIMENTAL PRODUCTION OF HYPERTENSION BY RENAL ISCHEMIA. However, a renal origin for essential hypertension as well was given renewed impetus when Goldblatt and his associates[44] induced pronounced and persistent hypertension, without renal excretory insufficiency, in dogs by bilateral constriction of the renal arteries. Subsequently renal hypertension was induced by Page[73] by investing the kidney with cellophane which formed a fibrocollagenous, compressing hull. The experiments of Goldblatt and his associates led to the concept that human essential hypertension, like the experimental form, might be the result of renal ischemia.

3. UNILATERAL RENAL ARTERIAL AND UROLOGIC DISEASE. Further support of the concept of a renal genesis of hypertension is found in the striking instances of hypertension following unilateral renal arterial occlusion, e.g., by embolism,[34] in cures of such cases of hypertension by unilateral nephrectomy, and in cases of unilateral urologic disease and hypertension in which the hypertension was cured by removal of the diseased kidney.[1, 96, 87, 101, 42a]

4. RENAL PRESSOR SUBSTANCES. Finally the demonstration of pressor substances related to the ischemic kidney in the experimental animal, and the similarity of the hypertension induced by such pressor substance to experimental renal hypertension and essential hypertension in humans, have also been advanced as evidence for the renal genesis of hypertension[74] (v. infra). Such pressor substances have not been demonstrated in the systemic blood of patients with essential hypertension.

5. RENAL ARTERIOLOSCLEROSIS IN ESSENTIAL HYPERTENSION. Renal arteriolosclerosis is almost universally present in autopsied cases of essential hypertension.[12, 33] While Fishberg[33] interpreted these findings as secondary to hyper-

tension, Moritz and Oldt[67] concluded that they were evidence of a primary diminution in renal blood flow and therefore supported the renal pathogenesis of essential hypertension. In a series of 100 renal biopsies taken in the course of sympathectomy for hypertension, Castleman and Smithwick[22] found that there was no vascular disease or only insignificant lesions in 28 per cent. They concluded that hypertension therefore preceded the development of renal arteriolosclerosis. Goldblatt[43] has objected that the small specimens taken do not necessarily reflect the vascular status of the entire kidney.

A more detailed discussion of the arguments favoring the renal mechanism of hypertension may be found in Goldblatt's[43] recent review and of the opposing viewpoint in a review by Smith, Goldring and Chasis.[102] Despite uncertainties as to the exact mechanism relating the kidney and hypertension, *the weight of evidence strongly suggests that the kidney is an important link in the pathogenesis of hypertension, essential or otherwise.*

Neurogenic and Humoral Factors in Hypertension. Since it has been long known that sympathetic vasoconstriction of the splanchnic vessels can elevate the blood pressure conspicuously, it was thought that the arteriolar constriction of human hypertension was due to this neurogenic mechanism. This viewpoint has been supported by the observation that a substantial fall in blood pressure follows sympathectomy in humans with hypertension.

On the other hand, there are many studies which seem to cast doubt on or minimize the importance of the sympathetic nervous system in the pathogenesis of essential hypertension. The observations of Prinzmetal and Wilson[85] indicated that the increased peripheral resistance in hypertension was not limited to the splanchnic vessels where sympathetic tonus is most concentrated. (But see also Abramson.[2]) The fall in blood pressure following sympathectomy in clinical hypertension is often absent, or insignificant or transient. Despite extensive sympathectomy the blood pressure is rarely restored to normal. A moderate fall in pressure after sympathectomy might denote merely the elimination of the normal vasoconstrictor element of the blood pressure without modification of the abnormal and excessive arteriolar tonus responsible for the hypertension.

In experimental renal hypertension a neurogenic factor has been excluded because: (1) total sympathectomy does not prevent or abolish the hypertension induced by constriction of the renal artery;[4] (2) transplantation of an ischemic denervated kidney to the neck of a different bilaterally nephrectomized dog induces hypertension[17] or hypertension may be induced by constriction of the renal artery after the kidney has been transplanted.[32] These experiments indicate that a humoral agent is responsible for the hypertension.

More direct support for a humoral mechanism of hypertension is provided by the finding of a number of substances which are believed to account for experimental renal hypertension. The following schema has been evolved:[74, 43, 25]

1. Renin[105] is an enzymatic substance formed in normal and hypertensive kidneys, which enters the blood stream through the renal vein and acts upon
2. Hypertensinogen (renin activator), an alpha globulin produced in the liver and found in the plasma, to produce
3. Hypertensin[69] (angiotonin[75]), a polypeptide which is a powerful pressor and vasoconstrictor. This can be inactivated by
4. Hypertensinase, an enzyme produced, among other organs, by normal kidneys and found in the blood.

Other pressor substances obtained from kidney have been suggested as pos-

sible agents in the mechanism of hypertension including the vasoexcitor material (VEM) of Shorr et al.[100] (p. 217) and pressor amines reported to result from defective deamination of amino acids in the anoxic kidney.[13, 71] An antibody to renin (antirenin), capable of neutralizing the pressor effect of an intravenous injection of renin, has been described.[106]

A causal relationship between these humoral agents and experimental renal hypertension is probable; their significance for human hypertension is hypothetical.

Other Etiologic Factors. AGE. Hypertension is uncommon before the age of twenty. Thereafter it is encountered in 20 to 25 per cent of the general population and in 40 to 60 per cent of those beyond the age of fifty.[65] Hypertension before the age of twenty occurs chiefly with coarctation of the aorta, acute or chronic glomerulonephritis and rarely with endocrine tumors.

SEX. Hypertension is slightly more common in the female, but hypertensive (and arteriosclerotic) heart disease is much more frequent in the male.

RACE AND ENVIRONMENT. An increased incidence of hypertension is often related to the accelerated tempo of modern industrialized civilizations. Negroes in Africa rarely suffer from hypertension,[27] but in the United States hypertension is more frequent and more severe in Negroes than in whites.[109] Similar observations have been made with respect to Chinese who emigrate to the United States.

HEREDITY. There is suggestive evidence of a familial tendency to hypertension;[7, 55, 84] it is said to be inherited as a dominant characteristic.[110] Statistical evaluation of small series of cases is difficult because of the frequency of hypertension in the general population.

CONSTITUTION. Hypertension has been related to body build and constitution.[90] It is commoner in the obese, and occurs with some predilection for the short, low-necked, stocky individual. There are certainly many exceptions. The hypertensive individual is characterized as a hyperreactor with exaggerated response to cold, epinephrine, etc.

TEMPERAMENT AND EMOTION. Psychologic disturbances have been postulated as initiating factors in hypertension. Transient, and occasionally permanent, hypertension has been found to follow repeated, powerful emotional experiences involving fear, anxiety and hostility, e.g., in the course of battle. A characteristic hypertensive personality[68] and distinctive psychiatric pattern[3, 14, 48a] have been described.

Pathologic Physiology

Circulatory Dynamics. The *cardiac output* is normal in uncomplicated hypertension.[21] Since the blood pressure is elevated, the *peripheral arterial resistance* must be *increased* to approximately the same degree.[10] The viscosity of the blood is altered insignificantly.

The increased peripheral resistance, due to widespread constriction of the arterioles and minute arteries, is the fundamental vascular alteration in essential hypertension. The arterial pressure rises because the volume flow of blood (cardiac output) in the arterial tree is unchanged while the capacity of the arterial tree is reduced by vasoconstriction.

That the heart is capable of maintaining its normal output despite the increased resistance to outflow is due to compensatory cardiac dilatation and hypertrophy (p. 10). If humoral substances, such as hypertensin, are con-

cerned in the pathogenesis of hypertension, these substances may aid in maintaining the normal cardiac output against increased peripheral resistance by increasing myocardial efficiency.

The *work of the heart in hypertension* can be calculated, though imperfectly, by multiplying the cardiac output and the mean arterial pressure.[88] The kinetic energy of ejection is ordinarily a negligible factor, but it may be more important in hypertension because of the increased velocity of ejection of blood.[111] Since the cardiac output is normal, the work of the heart is increased approximately in proportion to the elevation of arterial pressure.

The *circulation time* is normal in the absence of heart failure.

The *venous pressure* is normal as is the right atrial pressure measured directly by intracardiac catheterization.[16]

The *circulating blood volume* is normal in the absence of heart failure.

Mechanism of Cardiac Disease and Cardiac Failure in Hypertension. Cardiac disease and failure in hypertension may be due to:

(1) Increased work of the heart leading to cardiac dilatation and hypertrophy. The blood supply does not keep pace with the increase in muscle mass[51] and there is relative anoxia. This disparity is exaggerated with the development of coronary arteriosclerosis.

(2) Hypertension accelerates and intensifies the development of coronary arteriosclerosis (p. 342). The development of cardiac failure may be due predominantly to coronary insufficiency.

(3) With advancing hypertension, impairment of renal blood flow and renal excretory function become significant factors. A deficiency in the renal excretion of sodium and water would intensify any tendency to congestive heart failure.

Pathology

The essential cardiac abnormality is hypertrophy of the left ventricle.[70] In patients who succumb from noncardiac causes, dilatation is minimal (so-called concentric hypertrophy). This is probably due to the gradual evolution of the hypertension which permits effective hypertrophy to develop without apparent dilatation. The hypertrophy involves first the outflow tract (p. 25), or anterior half of the left ventricle, and later also the inflow tract.

In cases of hypertension with heart failure, dilatation and hypertrophy may both be pronounced. Although the left ventricle is predominantly affected, the right chambers may also be dilated and hypertrophied.

Coronary arteriosclerosis with or without severe narrowing and with or without occlusion and infarction is commonly present. Many of the pathologic findings in so-called hypertensive heart disease are due to arteriosclerosis of the coronary arteries (p. 345). Ischemic necrosis occurs in malignant hypertension.

Clinical Features and Course

Hypertension imposes a load on the heart which for many years may be compensated by left ventricular hypertrophy. Eventually, in more than half the cases, this compensatory mechanism is inadequate and congestive heart failure appears. Accordingly, hypertensive heart disease is often classified into two categories: (1) the compensated stage and (2) the decompensated stage.

Compensated Stage of Hypertensive Heart Disease. There are no symptoms referable to the heart unless there is advanced coronary arteriosclerosis. Angina

pectoris or an acute attack of coronary occlusion and myocardial infarction may occur. There may be symptoms of cardiac neurosis if the patient is aware of his hypertension.

The distinctive objective findings in the compensated stage of hypertensive heart disease are those related to left ventricular enlargement. This is analogous to the right ventricular hypertrophy in the compensated stage of chronic cor pulmonale.

Physical examination usually discloses no abnormality in the heart. Occasionally left ventricular hypertrophy is suggested by a forceful apical impulse, due partly to rotation of the apex nearer the chest wall and partly to a more forceful systolic contraction. The second aortic sound is often accentuated. Murmurs are absent, but an apical or basal systolic murmur may be caused by mitral or aortic sclerosis and calcification. In elderly patients with severe hypertension and pronounced dilatation of the ascending aorta, an "arteriosclerotic" aortic diastolic murmur is heard occasionally.[42]

Elongation of the aorta also leads to palpable pulsations in the jugular notch, while concomitant elevation of the subclavian, carotid and innominate arteries gives rise to strong arterial pulsations in the neck. The carotid arteries are occasionally distorted and kinked in such a manner as to produce localized pulsating bulges which may be mistaken for aneurysms.[19, 76]

Roentgen ray examination, including fluoroscopy, is often negative, but may disclose evidence of left ventricular enlargement. In the anteroposterior view there is rounding and increased convexity of the left ventricular contour (Fig. 6, p. 26). Later the apex is elongated downward to the diaphragm. Widening of the transverse diameter occurs with more pronounced degrees of cardiac enlargement.

When there is enlargement of the inflow as well as the outflow tract of the left ventricle, fluoroscopic examination of the heart in the left anterior oblique position discloses elongation and posterior displacement of the left ventricular contour. Consequently the latter encroaches on the retrocardiac space and may overlap the spine.

Increased pulsation of the aorta (dynamic dilatation) is not uncommon in hypertension. In cases of longstanding hypertension and aortic arteriosclerosis, elongation and elevation of the aortic shadow are frequently observed.

Electrocardiography. In 25 to 50 per cent of the cases of moderate hypertension, the electrocardiogram is normal. Often there is only a left axis deviation, but this may be absent even with the severe hypertension seen in the malignant or accelerated phase of essential hypertension.

The *characteristic findings* are those of left ventricular hypertrophy (Fig. 16, p. 38), namely: left axis deviation, high voltage of $R_1 + S_3$, depression of ST in lead I and low voltage or inversion of T_1 and occasionally also of T_2.[9, 64, 86, 91, 59, 52] There may be a slight elevation of ST_3, a slight prolongation of the QRS complex, and an abbreviation of the P-R interval.[94] Signs of left ventricular hypertrophy may be present without those of left axis deviation.

The presence of left ventricular hypertrophy may be revealed most clearly by multiple precordial leads (p. 40). The T wave is low or inverted in leads CF_4 and CF_5 and there is high voltage of the R.[30, 103a] High voltage of R with small or absent S in CF_4 or CF_5 and low R and deep S in CF_2 are indicative of left ventricular hypertrophy. A sudden transition from a low R in CF_3 to a tall R in CF_4 is especially significant. The frequent improvement or disappearance of

the hypertensive electrocardiographic pattern of left ventricular hypertrophy suggested to Bridges and associates[18] that the observed abnormalities were due to the hypertension, per se, and not to associated coronary or other myocardial disease.

Sometimes there are the characteristic alterations denoting bundle branch block[37] or intraventricular conduction defects, or there are other evidences of myocardial damage. These are not specifically related to the hypertension and usually represent cardiac impairment secondary to coronary arteriosclerosis.

Decompensated Stage of Hypertensive Heart Disease. Cardiac decompensation in the hypertensive heart is almost always associated with advancing coronary arteriosclerosis. The clinical picture is essentially similar to that described under arteriosclerotic heart disease. Details of the various clinical syndromes may be found under the headings of (a) angina pectoris, (b) coronary occlusion and myocardial infarction, and (c) congestive heart failure. Heart failure involves predominantly the left ventricle, but later there is evidence of congestion in the systemic as well as pulmonary circulation.

It is during the stage of heart failure that physical and roentgenologic examinations disclose pronounced cardiac enlargement. A systolic murmur due to functional mitral insufficiency, gallop rhythm and pulsus alternans are common. With extreme pulmonary congestion the second pulmonic sound may be louder than the second aortic despite systemic arterial hypertension. Auricular fibrillation is the commonest arrhythmia and occurred in 25 per cent of one series of 158 cases of hypertensive heart disease.[36] Not infrequently it appears to precipitate heart failure.

Diagnosis

The diagnosis of hypertensive heart in the compensated stage is based on the combination of persistent diastolic hypertension (above 90 mm. Hg) and evidence of left ventricular hypertrophy (roentgenologic and electrocardiographic).

The combination of diastolic hypertension and left ventricular hypertrophy together with evidence of (a) angina pectoris, (b) coronary occlusion and myocardial infarction, (c) congestive heart failure and/or (d) electrocardiographic signs of intraventricular conduction disturbances should justify a diagnosis of hypertensive and arteriosclerotic (coronary) heart disease if aortic stenosis is excluded.

As in cases of uncomplicated hypertensive disease an effort should be made to discover or exclude some renal, endocrine, vascular or neurologic cause of the hypertension.

Prognosis

The course and prognosis of hypertensive heart disease are conditioned chiefly by its cardiac complications, namely heart failure, acute coronary occlusion and myocardial infarction and angina pectoris. These are discussed under the headings named. However, hypertensive heart disease may be complicated, and its course abbreviated by noncardiac accidents. While 60 to 75 per cent of patients with hypertension eventually succumb from heart failure, acute myocardial infarction or a sudden cardiac death, about 15 per cent die of cerebral thrombosis, 5 to 10 per cent of uremia and the remainder of incidental causes such as carcinoma, pulmonary embolism or infection.

There is still uncertainty as to the exact duration of hypertensive heart dis-

ease, but survival for ten to twenty years is not unusual.[89, 38, 15] In the malignant phase of hypertension, characterized by diastolic pressure of 130 mm. Hg or more, neuroretinitis (hemorrhages, exudates and papilledema) and progressive renal insufficiency, the outlook is poor and death occurs within a year or two, but occasionally there are longer periods of survival. Whether some of the newer therapeutic procedures, especially sympathectomy, can prolong life and otherwise favorably alter the prognosis of hypertensive heart disease remains to be seen.

Treatment

Cardiac Manifestations. The treatment of heart failure, of angina pectoris and of acute coronary occlusion is discussed in Chapters 9, 18 and 21 respectively.

Control of Hypertension. Treatment is discussed chiefly from the viewpoint of alleviating cardiac strain in order to prevent or control heart failure.

Correction of Underlying Causative Disease. Remediable causes of hypertension should be sought. Surgical removal of a pheochromocytoma or of a pituitary or adrenal cortical tumor, correction of coarctation of the aorta and relief of urinary obstruction may reduce or abolish hypertension. Unilateral nephrectomy occasionally affords a brilliant cure of hypertension as well as of a urologic condition,[63] but unless the urologic status demands it nephrectomy is rarely indicated for the hypertension alone.[87]

General Treatment and Drugs. Adequate rest, relaxation and sleep are essential. Occasionally bed rest for a week or two may be valuable when the blood pressure rises to critical levels. Elevation of the head of the bed with 12 inch blocks may be desirable during bed rest if there is severe headache.

Psychotherapy, including reassurance and readjustment of the patient's attitude and way of life, is valuable.

Mild sedatives, such as the barbiturates, bromides or chloral hydrate, are the drugs most widely used in hypertension. They are indicated for clinical symptoms and not for the reduction of hypertension, per se.

Thiocyanate (sulfocyanate) causes a significant reduction in blood pressure, as well as an alleviation of symptoms, in more than 50 per cent of cases.[40, 62, 11, 66] Nevertheless its therapeutic usefulness is not generally accepted, and because of its toxicity, its administration must be regarded as experimental and possibly hazardous. The dosage is adjusted to maintain a thiocyanate level of 8 to 12 mg. per 100 cc.[8] Two capsules of potassium thiocyanate (each 0.2 gm.) are given daily. Blood levels are taken after three days if possible, and certainly at the end of a week. Dosage is modified accordingly, until the desired blood level is obtained. Thereafter the maintenance dose is determined; it is usually 0.2 to 0.4 gm. daily, but varies considerably. A 4 per cent official elixir of sodium thiocyanate N.F. is available. One dram (teaspoonful) contains 0.15 gm. Blood levels and blood pressures are checked every two weeks at first, and then once a month.

Toxic symptoms occur commonly, sometimes even with blood levels between 8 and 12 mg.,[61] but especially above 15 to 20 mg. per 100 cc.[107, 93, 28] The commonest mild symptoms are fatigability and weakness, cramps in the legs, pain in the feet, papular dermatitis or purpura, irritability, conjunctivitis, nausea, and occasionally thyroid enlargement and hypothyroidism. Rarely, and especially with uncontrolled dosage and excessive blood levels, serious compli-

cations occur, including severe gastrointestinal symptoms, exfoliative dermatitis, shock, delirium, convulsions, coma and death.

Numerous other drugs, including nitrites,[108] iodides, xanthines, hepvisc, renal extracts, vitamin A, tyrosinase, quinones, methylene blue and sympatholytic drugs, are either of insignificant merit or still experimental.[29, 58] Interest has recently been revived in the use of veratrum viride in the treatment of hypertensive crises and hypertension complicated by heart failure.[41] *Tetraethylammonium bromide* (or chloride) has been used in hypertensive cases as a preoperative test to select patients for sympathectomy rather than as a direct form of treatment. However, it has been found useful in the treatment of hypertensive heart failure in which it has relieved paroxysmal dyspnea and orthopnea due to pulmonary congestion or edema.[53]

Diet Therapy. Weight reduction is desirable for the obese and is often associated with some fall in blood pressure, but the results are rarely impressive.[48]

Low sodium diets, recommended over forty-five years ago,[5] have recently regained their popularity. The diets should contain less than 200 mg. of sodium daily, as described in the chapter on heart failure. Evidence has been adduced of a possible relationship of sodium to hypertension[81] and of the value of extreme sodium restriction for the reduction of high blood pressure.[50, 95]

Kempner[60] recommended the so-called rice diet (300 gm. of rice, 20 gm. of protein, but no animal protein, 5 gm. fat, 150 mg. sodium, carbohydrates in the form of fruits or fruit juices to make 2000 calories, 1 liter of fluid daily, vitamin supplements). On this regime, Kempner observed a significant reduction in blood pressure in the majority of hypertensive patients as well as a decrease in the size of the heart, a disappearance of electrocardiographic abnormalities and improvement or disappearance of retinal abnormalities. The merit of this diet probably depends on its very low sodium content, because equally good results were obtained with a daily allowance of 70 gm. of protein, including animal proteins, but with sodium restricted to 200 mg. daily.[20] Many of the hypotensive and other effects of the rice diet are similar to those following severe undernutrition. A pronounced loss of weight occurs commonly in patients on the rice-fruit regime.

I have also observed rapid significant reductions in the blood pressure of patients with severe hypertension when desalting was effected by daily injections of mercurial diuretics as well as by a low sodium intake.[104] But azotemia may develop despite sodium and water diuresis. A significant reduction in plasma volume occurs after a few days, and this may be concerned with some of the clinical effects. Resins have been administered with food in order to adsorb sodium.[26]

Sympathectomy. More or less extensive sympathectomies have been performed to eliminate or reduce the neural component responsible for increased splanchnic, arteriolar vasoconstriction in hypertension. Peet performs a bilateral supradiaphragmatic splanchnicectomy and lower dorsal ganglionectomy in a single stage procedure.[79] Smithwick[103] performs a bilateral lumbodorsal splanchnic sympathectomy, removing the great and lesser splanchnic nerves, dividing their aortic branches, excising the sympathetic trunk and interrupting their rami communicantes from D6 to L2. The operation is performed through a posterior, transdiaphragmatic approach in two stages, usually with a ten day interval between stages. An even more extensive sympathectomy is carried out by Grimson.[49]

Beneficial and sometimes striking results have been reported in a majority of operated patients with these procedures.[92, 56, 77, 24a, 49a] Reduction in blood pressure, disappearance of severe retinal abnormalities with improvement or return of vision, elimination of intractable headache and restoration of gainful occupation have been noted. A prolongation of life for patients in the serious malignant phase of hypertension has also been reported.[78] It is interesting to note the frequent reversal or disappearance of cardiac abnormalities, including cardiac enlargement, electrocardiographic evidence of left ventricular hypertrophy as well as gallop rhythm, pulsus alternans and recurrent left ventricular failure.[18, 57, 111a]

The operation has been criticized as being at most a palliative procedure of desperation, of unproven advantage over medical therapy, unphysiologic and without effect on the basic cause of hypertension.[39, 46] Disadvantages include an operative mortality of 1 to 5 per cent or more, considerable postoperative morbidity, a relatively long period of hospitalization and convalescence in the Smithwick[103] procedure, annoying postural hypotension for several months, neuritic pain for months, frequent loss of ejaculation in the male but not impotence, and uncomfortable sweating in areas supplied by the unoperated sympathetic fibers. The operation is contraindicated in the presence of azotemia, very recent myocardial infarction, or cerebral accident and uncontrolled heart failure. On the other hand alleviation of the hypertensive factor may eliminate the manifestations of heart failure as well as other clinical complications.[22a]

The surgical indications vary with different physicians. Some recommend the performance of sympathectomy in relatively early cases in order to prevent later irreversible cardiac, cerebral or renal damage. For the present this view is not justified since most hypertensive patients have a relatively favorable course and the ability of sympathectomy to prolong life and prevent complications is unproved. I believe, therefore, that sympathectomy should be reserved for patients with severe and progressive manifestations who do not respond to medical therapy, as outlined above. Usually I recommend the procedure to patients with severe hypertension (diastolic pressure 130 or over) who suffer from intractable headache or severe fundal changes despite medical therapy. Both of these manifestations are almost always relieved or eliminated by sympathectomy, whether or not there is a significant fall in blood pressure. In addition I recommend the procedure to patients in the malignant phase of hypertension with apparently rapid progress of the disease and in those patients with a diastolic pressure of 130 or over who experience recurrent episodes of left ventricular failure. In a recent survey of 119 personally observed cases of hypertension in which sympathectomy was performed an average of thirty-two months earlier, Fishberg[35] reported that the operation was indicated in only 4 per cent of his hypertensive patients, and that a 25 per cent or greater reduction in diastolic pressure was effected in 25 per cent of the cases.

THE HEART IN RELATION TO RENAL DISEASE

Acute Glomerulonephritis

There are four important manifestations of acute glomerulonephritis which are of special interest to the cardiologist: (1) hypertension, (2) cardiac enlargement, (3) electrocardiographic evidence of myocardial involvement and (4) congestive heart failure.

Hypertension is a cardinal feature of acute diffuse glomerulonephritis and occurs at the onset of the disease. The rise in blood pressure is almost always moderate and usually does not exceed 180/100, except with encephalopathy.

Cardiac enlargement appears early, probably within the first week or two.[122] The enlargement is relatively mild, but may be considerable in the presence of pronounced congestive heart failure. Serial roentgen ray examinations disclose a return to normal cardiac size with subsidence of the disease.[112] Occasionally cardiac enlargement persists despite normal blood pressure.[118] Hypertrophy as well as dilatation of the left ventricle is observed at autopsy.[125]

The cardiac enlargement has generally been attributed to the hypertension but it has been observed in the absence of significant hypertension, and the degree of enlargement is usually out of proportion to the mild elevation in blood pressure and its brief duration. Gore and Saphir[123] found evidence of a serous myocarditis with sparse cellular infiltration in 16 of 160 anatomically proven cases of acute and subacute glomerulonephritis. They attributed both cardiac hypertrophy and failure to the myocarditis. On the other hand I have observed pronounced cardiac enlargement and hypertrophy only in association with heart failure and it has appeared to me that it is the heart failure which, in accordance with Starling's law of the heart, is responsible for the enlargement.

Electrocardiographic abnormalities occur frequently, but they are mild and may not be observed except after repeated examinations. Low or inverted T waves in lead I and in the precordial leads are the commonest changes.[140, 132, 113] Prolongation of the P-R interval and of the Q-T interval also occurs. According to La Due and Ashman,[131] right deviation of the Wilson gradient is a common abnormality and denotes relative ischemia of the left ventricle.

Congestive heart failure is the most important, most serious and most frequent complication[134, 120, 144, 151, 142, 114] of acute glomerulonephritis. Heart failure has been attributed to the strain of the hypertension, and to myocardial damage as indicated by electrocardiographic and anatomic changes. But the elevation in blood pressure appears too slight and brief and the electrocardiographic and anatomic changes too minor to be significant, and there is often no correlation between the degree of hypertension and the presence or severity of heart failure.[134, 142, 151] The heart failure appears to me to be due to a relative deficiency in the renal excretion of sodium and water. It appears most frequently when oliguria is severe and is usually induced by overenthusiastic parenteral administration of sodium-containing fluids to combat vomiting and promote diuresis. This explanation does not exclude the possibility that hypertension and myocardial edema—"serous myocarditis"—are secondary accessory factors in the accentuation of myocardial disability.

Heart failure may be characterized by a sudden onset of dyspnea and orthopnea, often progressing to acute pulmonary edema. But frequently it appears more gradually. Tachycardia, muffled cardiac tones, an apical systolic murmur, gallop rhythm and râles at the bases of the lungs are common with left ventricular failure. But heart failure may develop more insidiously and may involve the systemic as well as the pulmonary circulation. Pleural effusion is common and is part of the general anasarca. Recent evidence indicates that renal edema fluid does not differ essentially in composition from that of cardiac edema and may have a similar pathogenesis.[150] A high venous pressure was found regularly in La Due's cases,[130] but the circulation time was normal. The edema of nephritis, like that of heart failure, may not be caused by an intrinsic disturbance in

capillary permeability, but by an elevated hydrostatic pressure and a diminution in osmotic pressure due to low plasma proteins.

The *treatment* of acute glomerulonephritis should be primarily directed to the prevention or abolition of heart failure, which is always present or a potential danger. Sodium intake should be avoided if there is severe oliguria and should not exceed 200 mg. daily until normal urinary output and concentration are restored. The parenteral administration of fluids is hazardous until that stage is reached. During the acute phase, an allowance of 500 to 1000 cc. of fruit juice, orally, is permissible as the total diet. Thereafter one may shift to the rice-fruit-fruit juice regime as advocated by Kempner until renal function is restored. In the presence of heart failure, digitalis in a rapidly excreted form should be given (e. g., cedilanid, digoxin). Mercurial diuretics should not be administered.

Toxemia of Pregnancy

The findings in the heart and circulation in toxemia of pregnancy resemble very much those described for acute glomerulonephritis.[147]

Lower Nephron Nephrosis

Under the heading of lower nephron nephrosis[135, 137] are included renal diseases characterized by tubular degeneration and necrosis with subsequent regeneration, frequent pigment deposits in the tubules, and interstitial inflammation but no visible glomerular alterations. The disease may be caused by a wide variety of agents which induce prolonged shock, renal ischemia and anoxia or allergic and toxic damage to the tubules. Some of the best known causes are: (1) extensive burns[139] or wound shock, especially the crush syndrome,[115, 117] (2) hemoglobinuric nephrosis due to mismatched blood, (3) sulfonamides,[141] (4) carbon tetrachloride inhalation,[145, 129] (5) blackwater fever and other factors responsible for intravascular hemolysis of erythrocytes, (6) hyperthermia and various poisons.

From the cardiovascular viewpoint, the important features are the acute development of extreme oliguria or anuria and hypertension, and the invariable danger and frequent occurrence of congestive heart failure. Cardiac dilatation, gallop rhythm, pulmonary congestion and hydrothorax, subcutaneous edema and ascites are common. Death is often due to acute pulmonary edema. Almost invariably the development of heart failure is precipitated by the parenteral administration of fluids in an effort to alleviate vomiting, promote diuresis or maintain fluid or electrolyte balance. Intracellular breakdown contributes extensively to the excess of extracellular volume. Both of these factors are important because there is no urinary output at all or only an insignificant amount. Similar clinical evidence of left ventricular failure may be precipitated by parenteral sodium-containing fluids in postoperative patients[116] and patients with toxemia of pregnancy[149] whose urinary output is very small.

Treatment should consist of 500 to 1000 cc. of fruit juice by mouth, if tolerated. The parenteral administration of fluids is interdicted until there is a good urinary output and improving renal concentration with a falling blood urea. Peritoneal irrigation,[121] artificial kidney[128] or similar therapies[145a] may be considered during the period of anuria and extreme azotemia. Usually toward the end of the second week a more liberal oral intake is permissible, but not more than 200 mg. of sodium daily (e. g., Kempner regime). When

the blood urea is falling and diuresis is pronounced, a cautious restoration of acid-base and electrolyte balance should be undertaken (by oral or parenteral routes). However, this may be unnecessary when the basic renal lesion is healed, renal function is restored and a normal diet is permitted. In the presence of oliguria or anuria, digitalis should be given cautiously, even when heart failure is present. Cedilanid by injection or digoxin orally is preferred because of rapid elimination, but the usual dosage should be diminished to allow for deficient excretion and to avoid the danger of redigitalization when active diuresis occurs. Mercurial diuretics are interdicted. In some instances, if the patient is seen early during the stage of shock and if there is a low blood volume, the cautious administration of blood, plasma or saline is indicated. As a rule lower nephron nephrosis is a spontaneously reversible condition in which diuresis begins two weeks after onset, independent of treatment.

Chronic Nephritis and Uremia

Cardiac manifestations are uncommon until the stage of advanced renal insufficiency and uremia.[143] Hypertension is less prominent than in cases of essential hypertension, but occasionally the blood pressure and clinical features are indistinguishable from those of the malignant phase of essential hypertension. Coronary arteriosclerosis is less frequent than in essential hypertension, probably because most patients with chronic glomerulonephritis succumb before the age of forty. In the cases of nephritis with hypercholesterolemia, the coronary atherosclerotic process is said to be precocious.

Heart failure is uncommon except toward the end of the disease. It results from deficient excretion of sodium and water, the intravenous administration of excessive quantities of fluids, and occasionally from associated hypertension, coronary arteriosclerosis and anemia.

In the presence of *uremia,* a sterile pericarditis occurs commonly, possibly due to retained metabolites.[146] While the pericarditis is often a terminal manifestation, it may appear many weeks before the end, may undergo remission and recurrence and may even heal.[127] Extreme retention of potassium may cause ventricular standstill or fibrillation and death.[138]

The heart in uremia may show not only pericarditis but also foci of fatty degeneration and vacuolization of muscle fibers, which have been likewise attributed to metabolic toxins.[124] Lüscher[136] described a case in which there was severe interstitial hemorrhagic myocarditis.

Roentgen ray films of the chest show no abnormality or the left ventricular enlargement associated with hypertension. Occasionally there are striking pulmonary changes characterized by bilateral clouding of the central and lower median lung fields, which may appear and disappear in a few days (azotemic edema of the lungs).[119] They are due to pulmonary edema caused by left ventricular failure.

Electrocardiographic changes occur often in uremia. There are frequently evidences of left ventricular hypertrophy and of myocardial damage in the cases associated with severe hypertension and coronary arteriosclerosis. More distinctive are[152, 133, 148]:

(1) T wave inversions with or without ST elevations due to diffuse pericarditis[127];

(2) Prolongation of the Q-T interval due to hypocalcemia;

(3) Tall narrow T waves in limb and chest leads with early hyperpotassemia,

bizarre slurring, notching and widening of the QRS complexes,[126] and bradycardia with or without intraauricular and auriculoventricular block with more advanced potassium intoxication, and finally, cardiac arrest.[138] A deep Q wave and abnormal ST elevation in CF_2 and a tendency of P_3 to disappear have also been noted.[148]

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38

ACUTE COR PULMONALE AND PULMONARY EMBOLISM

DEFINITION

Pulmonary heart disease or cor pulmonale refers to the cardiac and circulatory disturbances resulting from disease of the lungs, the pulmonary artery or its branches.

Pulmonary heart disease has been divided into acute and chronic forms, the so-called acute and chronic cor pulmonale. *Acute cor pulmonale*[60] includes cases of sudden pulmonary vascular obstruction due to massive or extensive pulmonary emboli. However, acute cor pulmonale and pulmonary embolism are not interchangeable terms, for only massive or extensive embolization is usually capable of producing cardiac disease. *Chronic cor pulmonale* (Chapter 39) includes cases in which cardiac abnormalities result from gradual and longstanding pulmonary vascular obstruction due to certain bronchopulmonary diseases, to kyphoscoliosis or to primary or secondary diseases of the pulmonary arteries or arterioles.

The occurrence of pulmonary embolism following operation is well known but it is less generally recognized that it appears with equal or greater frequency among medical patients.[11, 16] Thus of 370 autopsied cases of pulmonary embolism and infarction, Hampton and Castleman[41] found that 40 per cent represented a postoperative complication, but 30 per cent were cardiac medical cases and another 30 per cent noncardiac medical cases.

Pulmonary embolism is closely related to the subject of heart disease, not only because it may produce so-called acute cor pulmonale, but also because it produces symptoms which may be confused with those of acute coronary artery occlusion[39, 3] and because it is a common complication of congestive heart failure.

ETIOLOGY

The *direct cause* of acute cor pulmonale is a rapid obstruction of the pulmonary circulation by one or more large antemortem blood clots (emboli), which arise in a thrombus of the systemic veins or right chambers of the heart. As a rule, the embolus is of the bland (noninfected) variety.

An important *predisposing factor* is a period of complete bed rest, often with great immobilization of the body. However, pulmonary embolism may

occur also among ambulant persons.[42] Pulmonary embolism occurs after operations, parturition, fractures and other serious injuries. It also occurs in patients with cardiac disease, especially when complicated by failure, and in patients with carcinoma, disease of the veins of the lower extremities and hematologic diseases.[6] Among operations, pulmonary embolism most frequently follows those on the pelvic organs in the female and on the prostate in the male, but it may occur after almost any operation. The embolism may occur as early as the first postoperative day, but more than half occur in the second and third weeks.

Age and Sex. Pulmonary embolism may occur from youth to old age, but most instances are encountered in patients beyond the age of forty.[1] There is no significant difference as to frequency among the sexes. According to Barker and his associates[6] the majority of cases occur between the ages of forty and sixty among females, between fifty and seventy among males.

Precipitating Factors. Not infrequently symptoms of pulmonary embolism appear during or immediately after straining at stool, getting out of bed, or getting in and out of a wheel-chair.[56] It is probable that these factors aid in dislodging a thrombus into the circulation.

PATHOLOGY

Venous Thrombosis. The source of pulmonary embolism is almost always a thrombus in the veins of the lower extremities.[92a] These thrombi form in the deep veins of the calf muscles[75, 47] and perhaps also in the plantar veins.[67] Thrombi in the veins of the thigh and iliac region arise by extension of these more peripheral thrombi. Occasionally the thrombi responsible for pulmonary emboli arise in the periprostatic or other abdominal veins or right cardiac chambers and rarely in the veins of the head, neck, upper extremities or trunk. Sometimes no thrombotic origin of the embolus is found, either because the whole thrombus is detached or because of incomplete or inadequate postmortem examination.

The venous thrombi which give rise to pulmonary emboli are often bland and asymptomatic[45] and may be easily overlooked.[21, 47] These have been classified as *phlebothrombosis*[69] in contrast with the thrombi which are characterized by severe pain, edema and swelling of the extremity and are classified as *thrombophlebitis*. The latter thrombi infrequently cause pulmonary embolization because they are firmly attached to the vein, except in the first day or two before they are fully adherent.[6] Thrombophlebitis may be associated with asymptomatic deep venous thrombosis in the same or opposite extremity.

For a discussion of the pathogenesis of venous thrombosis the reader is referred to the publications of Welch,[89] Hampton and Wharton,[43] Baumgarten,[10] Dietrich[25] and Ochsner.[68] Slowing of the blood stream,[81] injury to the vascular endothelium and alterations in the physical or chemical properties of the blood which promote coagulation are among the most important causative mechanisms.

Pulmonary Emboli. Pulmonary emboli which cause important cardiac and circulatory sequelae and usually death are of massive size and obstruct the main pulmonary artery or its major branches. The emboli attain great size by coiling up until they form large masses by the time they reach the pulmonary artery. When the embolus is unfolded it may be restored to its original form, often with a length of 15 to 30 cm. or more.

In instances of sudden death or of severe shock and death within minutes or hours, the embolus usually occludes completely or almost completely the main pulmonary artery or both its primary branches. When the embolus blocks the main pulmonary artery, it sometimes extends to the conus of the right ventricle and partially occludes the pulmonary valvular orifice (functional pulmonary stenosis). More often there is a riding embolus at the bifurcation of the pulmonary artery with complete occlusion of one branch and incomplete occlusion of the other. Part of the embolus may appear older than the rest and organized, as if the original embolus were enlarged by a later embolus or local thrombosis. Often the pulmonary clots are multiple and represent emboli which have migrated at intervals rather than all at once.[11]

Single emboli in one large pulmonary arterial branch or multiple emboli in small branches are infrequently fatal and only occasionally cause significant general circulatory sequelae. They are, however, often associated with pulmonary infarction and local pleuropulmonary manifestations.

The Heart. The effect of pulmonary embolization on the size of the heart is difficult to evaluate postmortem, unless dilatation is very striking. However, dilatation of the pulmonary artery and right cardiac chambers has been observed following the experimental production of pulmonary obstruction or embolization in animals and during surgical attempts to remove the embolus in humans.[60, 18]

Pulmonary Infarction. Lesser degrees of pulmonary embolism are usually followed by pulmonary infarction. It has long been noted that cardiac failure with prolonged pulmonary congestion, such as occurs particularly with mitral stenosis, is a major predisposing factor in pulmonary infarction. It has been demonstrated experimentally[51, 16a] that infarction followed pulmonary arterial embolism only when pulmonary congestion was previously produced by ligation of the corresponding vein or by compression of the lung by instilling fluid into the pleural cavity. The development of pulmonary infarcts depends also on the size of the vessel occluded by the embolus. Obstruction of the main pulmonary artery or most of both primary branches may cause death within minutes or hours before an infarct can develop. In the experiments of Karsner and Ash, three to forty-eight hours elapsed before the appearance of infarction. If very small vessels are occluded, infarction may not develop because of wide capillary anastomoses and collateral circulation from the bronchial arteries. An infarct is most likely to result if a medium-sized or large pulmonary artery branch is occluded, if there is preexisting pulmonary venous stasis and if the patient survives at least for a day or two. It is important to recognize that acute cor pulmonale may occur with or without pulmonary infarction. Conversely pulmonary infarction does not necessarily denote the presence of acute cor pulmonale nor does the absence of infarction preclude the existence of massive pulmonary embolism with circulatory sequelae.

PATHOLOGIC PHYSIOLOGY OF PULMONARY EMBOLISM

It has long been known since the experiments of Welch,[89] Cohnheim[19] and others that there were no serious circulatory disturbances and no fall in systemic arterial blood pressure after pulmonary arterial constriction, unless the latter became extreme. Then the venous pressure rose, the systemic arterial blood fell precipitously and death ensued unless the constriction was removed. More recent quantitative studies[37, 62, 34] have demonstrated that until 50 to

65 per cent of the pulmonary cross-sectional area is cut off there is no significant effect on systemic arterial or venous pressure. Death usually follows more than 85 per cent obstruction.

Intermediate grades of pulmonary artery obstruction, insufficient to cause death or a sharp reduction in systemic arterial blood pressure, may nevertheless raise the pressure in the pulmonary artery and right ventricle.[37] Fineberg and Wiggers[28] found that following pulmonary compression which did not exceed 58 per cent of the cross-sectional area, the increased pulmonary resistance was compensated by a rise in right ventricular pressure which led to a stronger right ventricular contraction, sufficient to maintain a relatively normal supply of blood to the left ventricle. These experimental observations suggest that, in humans, pulmonary embolism of less than massive size which is insufficient to produce general circulatory disturbances may nevertheless cause right ventricular strain.

PATHOGENESIS OF CIRCULATORY AND CARDIAC SEQUELAE

The circulatory and cardiac disturbances which follow large pulmonary emboli have been attributed to: (1) the mechanical interference with cardiac output, and (2) myocardial ischemia.

1. The *mechanical effects* of pulmonary emboli have been described under pathologic physiology. Very large emboli interfere sharply with the output from the right heart, consequently diminish the inflow into and output from the left ventricle so that aortic pressure is markedly reduced and the evidences of shock appear. At the same time, the increased pulmonary resistance causes strain on the right ventricle which may lead to dilatation and perhaps backward failure of the right cardiac chambers. The above-mentioned experiments, which demonstrate that the various circulatory disturbances result only after a major portion of the cross-sectional area of the pulmonary circulation is occluded, and that the seriousness of the circulatory effects is roughly proportional to the degree of occlusion, form the strongest evidence for the belief that the mechanical obstruction to the circulation is the direct and primary cause of the circulatory sequelae of massive pulmonary embolism.

2. *Myocardial ischemia* has been invoked to account for sudden death in some cases, and to explain certain similarities in the clinical and electrocardiographic pictures of pulmonary embolism and acute myocardial infarction. Three mechanisms may account for the occurrence of myocardial ischemia after pulmonary embolism.

(a) Massive pulmonary embolism causes a reduction in left ventricular output and aortic pressure, with a corresponding diminution in the blood supply to the coronary arteries.

(b) Arterial anoxemia due to pulmonary asphyxia may produce anoxia of the myocardium.

(c) Reflex vasoconstriction of the coronary arteries, mediated by the vagus nerves (pulmonocoronary reflex), has been suggested to account for the occurrence of sudden death, in cases in which there were only relatively small pulmonary emboli.[76, 55] Receptors for vagal reflexes have been demonstrated in the pulmonary artery.[77] Experimentally, preliminary vagotomy or the administration of atropine permitted a high incidence of survival in animals injected with a lethal dose of pulmonary emboli.[76, 85] However, other experiments have not substantiated these findings and have failed to support the

theory that death from pulmonary embolism is due to pulmonary reflexes to the heart or respiratory center.[59, 38]

Serious circulatory disturbances or death following relatively small pulmonary emboli have also been explained by assuming that local reflex vasoconstriction enhances the obstructive effect of the embolus. This is analogous to the well known vasoconstriction following embolization of a peripheral artery in an extremity. However, while there is strong vasomotor control of the peripheral vessels there is considerable disagreement as to the importance of vasomotor effects in the pulmonary vessels.[23, 40]

(d) Coronary blood flow may be restricted by the rise in pressure in the right cardiac chambers[88] following pulmonary embolism. This rise in intraventricular pressure diminishes the effective coronary pressure head and impairs drainage by way of the thebesian vessels.

Whatever the causes of myocardial ischemia may be in cases of massive pulmonary embolism, its occurrence appears substantiated by the clinical-pathologic studies of Friedberg and Horn[30] and of Horn, Dack and Friedberg.[46] In 8 of 42 autopsied cases of pulmonary embolism the latter observers found acute or subacute myocardial necrosis, similar to that seen in cases of acute myocardial infarction due to recent coronary occlusion. The structural changes, which were most severe in the subendocardial region of the left ventricle, were interpreted as occurring only when myocardial ischemia was sufficiently severe and prolonged. The development of necrosis was favored by a duration of life for several hours or weeks after the initial embolism, by preexisting coronary sclerosis and narrowing, and by previous hypertrophy of the heart which accentuated any coronary insufficiency. However, in three cases myocardial necrosis occurred in the absence of significant narrowing of the coronary arteries.

CLINICAL FEATURES

Onset and Premonitory Symptoms

The characteristic *onset* of massive pulmonary embolism is sudden and without warning. Not infrequently, however, a review of the history or of the nurse's notes reveals premonitory symptoms and signs, which are due to small emboli occurring hours or days before the final massive one.[86]

Acute dyspnea or tachypnea, cyanosis and chest pain occur frequently. Weakness is common. In addition there may be abdominal pain, substernal fullness, hemoptysis, faintness or fainting, dizziness, restlessness, mental symptoms or convulsions at the onset or as premonitory signs. Only one of the above symptoms may be present. Quite often a rise in temperature and tachycardia are the only apparent clinical manifestations. Or the pulmonary embolism may be documented by a paroxysmal arrhythmia. The symptoms of pulmonary embolism may be overshadowed by the underlying cardiac or other disease or by infection and postoperative complications.

The clinical manifestations are determined by four factors: (1) a diminished cardiac output, (2) acute pulmonary hypertension with strain or failure of the right ventricle, (3) diminished pulmonary aeration and (4) pulmonary infarction.

1. Manifestations Due to Diminished Cardiac Output. The sudden occlusion of a major portion of the pulmonary circulation sharply reduces the output of

the heart and results in the clinical features of acute circulatory failure (shock). With extreme obstruction death is instantaneous or within a few minutes after the patient cries out. Death is probably due to cerebral anoxia. In instances of sudden death with relatively small pulmonary emboli, ventricular fibrillation may be the responsible mechanism. There may be a relatively brief period of air hunger, great restlessness and anxiety or oppression or pain in the anterior chest. Chest pain, resembling that of angina pectoris or coronary occlusion, may in fact be due to severe myocardial anoxia. Mental symptoms, ocular palsies, convulsions and coma may result from a depletion in cerebral blood flow. Syncopal manifestations are usually irreversible, but occasionally they are followed by recovery. When death does not occur within a few minutes or hours, shock is manifested by weakness and mental apathy, cold, moist extremities, pallor or ashen cyanosis, a weak rapid pulse and a fall in blood pressure.

2. Manifestations Due to Right Ventricular Strain and Failure. Certain of the manifestations of massive pulmonary embolism may be attributed to the pulmonary hypertension following the arterial obstruction and to the consequent acute strain or failure of the right ventricle. The term acute cor pulmonale is limited to these signs of acute right ventricular strain. In the cases I have observed, the signs of acute right ventricular strain were usually associated with or overshadowed by those secondary to a diminished cardiac output.

Pulmonary hypertension may be denoted by accentuation of the second pulmonic sound. A dilated pulmonary artery may be disclosed by increased percussion dullness in the second left interspace and sounds resembling a friction rub in this region.

The occurrence of a systolic thrill and loud murmur over the pulmonic area, due presumably to stenosis of the pulmonary orifice caused by the embolus, has been reported by Litten[56] and others. In one of the patients with massive pulmonary embolism reported by Horn, Dack and Friedberg,[46] I heard a harsh, loud systolic murmur and felt a systolic thrill over a large area of the precordium. Postmortem examination revealed a coiled, tubular gray-red thrombus filling the main stem and most of the left branch of the pulmonary artery and extending proximally to the pulmonary orifice of the heart, which it occluded to a large degree.

Failure of the right ventricle after massive pulmonary embolism is an acute event and is indicated chiefly by engorgement of the cervical veins.[35, 92] Often this is accompanied by vasoconstriction of the peripheral veins in the extremities, apparently as a compensation for the diminished cardiac output. Acute enlargement of the liver may result from systemic venous engorgement. Occasionally right heart failure is denoted also by the presence of a gallop rhythm at the left of the midsternum. Peripheral edema and other signs of chronic congestive heart failure are absent. If the patient survives, the organization of the pulmonary emboli may produce sufficient permanent pulmonary obstruction to cause chronic pulmonary heart disease and even chronic right-sided congestive heart failure[12] (p. 905).

3. Manifestations Due to Deficient Pulmonary Aeration. Dyspnea and cyanosis are common manifestations of pulmonary embolism. A brief episode of dyspnea, with or without associated tachycardia and rise in temperature, is not infrequently the major symptom of a pulmonary embolism. Tachypnea, with shallow or deep breathing, is a common form of respiratory abnormality.

These disturbances in respiration may be initiated by pressure changes within the lung and mediated through the vagus as exaggerated Hering-Breuer reflexes. The intrapleural pressure has been found to be elevated and the residual air increased.[14] Since dyspnea may be present while the arterial oxygen is normal, it is probably not due to chemical stimulation of the respiratory center.

On the basis of their experiments, Gibbon and Churchill[33] and Takats, Beck and Fenn[85] have described two forms of pulmonary embolism: (1) the syncopal, characterized by shock, fall in blood pressure and pallor and corresponding to an obstruction in the main pulmonary artery, and (2) the asphyxial, characterized by deep cyanosis as well as dyspnea and corresponding to obstruction of many large branches but not of the main pulmonary arteries. In my experience such a sharp distinction cannot be applied to human instances of pulmonary embolism. I have seen black-blue cyanosis in patients with massive pulmonary embolism who also presented signs of severe shock.

The presence or absence and the degree of cyanosis in various cases of large pulmonary embolism often cannot be explained. When cyanosis appears, it must be assumed that pulmonary aeration of the blood is deficient despite tachypnea, increased tidal volume and minute volume of respiration. When dyspnea occurs with little or no cyanosis, it is probable that despite the obstruction of the pulmonary blood supply aeration of the blood by the lung is adequate, due to a compensatory increase in minute volume of respiration.

4. Pulmonary Infarction. Pulmonary infarction is not a necessary consequence of pulmonary embolism, nor is it an essential part of the clinical picture of acute cor pulmonale. Its pathogenesis has been discussed above. However, pulmonary infarction associated with embolism of a medium-sized pulmonary artery frequently precedes a more severe obstruction which causes acute cor pulmonale or death.

Evidences of pulmonary infarction may not appear for at least twelve to twenty-four hours after the causative embolism. Due to pleural involvement there is often a sharp pain in the chest, neck, shoulder or abdomen, especially on deep inspiration. Cough with the expectoration of frothy sputum or bright red blood is a common symptom.[53] But hemoptysis may be absent. Fever and leukocytosis usually appear rapidly but both of these abnormalities may be minimal or absent. In cases of chronic heart failure, fever may be the only apparent manifestation of pulmonary infarction. Tachycardia is often present and there may be dyspnea or cyanosis. There are often signs of consolidation over the infarcted area or there may be only moist râles. Local tenderness is often elicited on percussion. A pleural rub is heard occasionally. Signs of effusion appear frequently.[36] The pleural fluid is usually an exudate, is often hemorrhagic and contains bile pigments. Occasionally a pulmonary infarct becomes infected and forms an abscess.[17, 72] In fatal cases, pulmonary edema may develop terminally. While these are the classic features of pulmonary infarction, there is considerable variation and the infarct may be entirely asymptomatic. In particular, chest pain, cough and hemoptysis are frequently absent.

Electrocardiographic Signs of Pulmonary Embolism

In 5 of their 7 cases of acute cor pulmonale in which electrocardiograms were taken early, McGinn and White[60] observed abnormalities which were fairly similar and which were interpreted as being characteristic of the condition. The chief abnormalities were:

1. A deep S_1.
2. Prominent Q_3 and inversion of T_3 as in myocardial infarction of the posterior wall.
3. Depression of ST segment in lead II and often in lead I and a staircase ascent of ST_2.
4. T_2 and T in lead IVF may be diphasic or inverted.

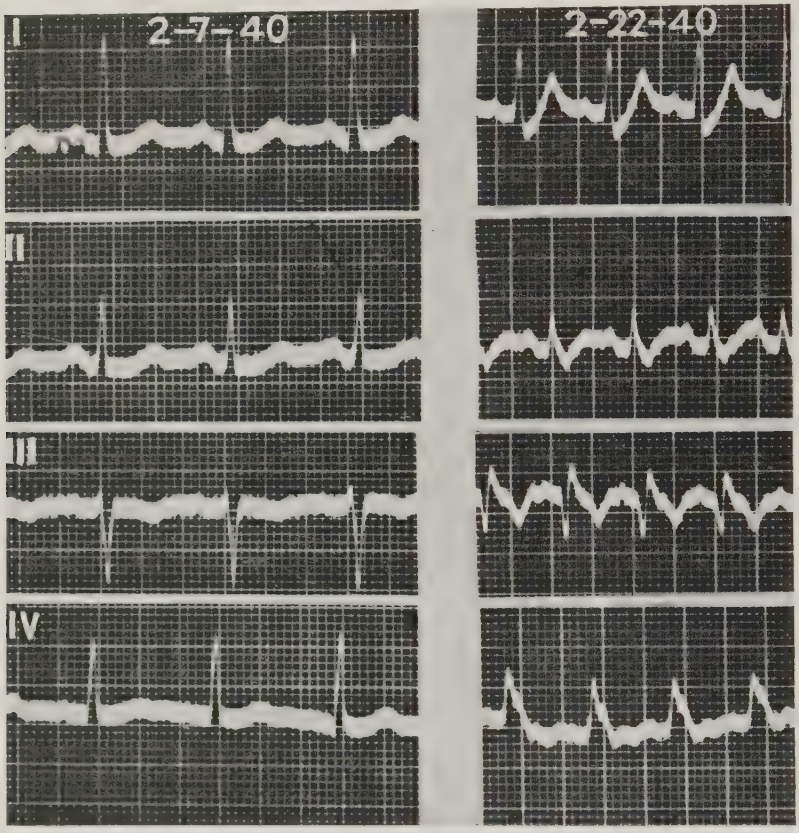


Fig. 73. *A,* Normal electrocardiogram. Left axis deviation.
B, S_1 type of right bundle branch block following acute pulmonary embolism.

5. Occasionally there was a right deviation of the electrical axis, but never a left deviation during the acute episode. The abnormalities disappeared in a few days.

Subsequent studies have confirmed these findings, with certain variations and amplifications.[76, 54, 27, 63] The abnormalities are found in only 10 to 20 per cent of cases of pulmonary emboli,[58, 82] chiefly because electrocardiograms are not taken early enough or because the emboli are too small to cause a strain on the right ventricle. In cases of pulmonary artery obstruction produced in the course of pneumonectomy in humans, the electrocardiograms showed a shift of the electrical axis to the right and a deep S_1 in the majority of instances. The changes appeared immediately and disappeared in twenty-four hours.[78] Durant, Ginsburg and Roesler[26] noted right bundle branch block with broad

shallow S_1 and S_2 in the first two hours after pulmonary embolism (Fig. 73). Occasionally P_2 is tall and sharp.[92] Frequently the electrocardiogram of pulmonary embolism is modified by preexisting abnormalities due to myocardial disease.

Multiple chest leads usually reveal the most persistent changes, for they may not disappear for three to six weeks. Wood[92] described an inversion of the T wave from V_1 to V_3 or V_4. Occasionally he observed a transient right bundle branch block (Fig. 73).

Clinical, experimental and electrocardiographic observations strongly suggest that the electrocardiographic changes are due primarily or exclusively to acute right ventricular strain following massive pulmonary embolism.[60, 59, 78] The possibility that myocardial anoxia is a contributing factor is suggested by



A B

Fig. 74. *A*, Pulmonary infarction left upper lobe.
B, Clearing of infarct with residual horizontal linear scars or focal atelectasis.

the Q_3 T_3 changes resembling those of posterior wall infarction and by the pathologic findings of myocardial necrosis in cases of massive pulmonary embolism.[30, 46, 22] However, the identical electrocardiographic abnormalities have been observed in cases without myocardial necrosis.

Roentgenology

The roentgenologic signs directly attributed to acute cor pulmonale either are not striking or have been insufficiently studied. The hilar shadows and pulmonary vascular shadows may be wider than normal. The left middle salient may be prominent due to dilatation of the pulmonary artery.

Roentgenologic study[80] may suggest the presence of pulmonary infarction resulting from pulmonary embolism. The shadows of pulmonary infarcts may not appear until twenty-four hours or several days after the occurrence of the pulmonary embolism. An early sign of pulmonary infarction, according to Wharton and Pierson,[91] is the clouding of the base of the lung, obscuring the costophrenic sinus on the affected side. Infarcts are often multiple and occur chiefly in the lower lobes.[74] The shadows of infarcts may have the classic tri-

angular shape (Fig. 74), but more often they are round, oval or irregular.[48] Often they are indistinguishable from pneumonic infiltrations or from severe pulmonary congestion due to heart failure. According to the studies of Hampton and Castleman,[41] infarcts occur most often at the junction of two pleural surfaces and therefore the roentgen ray shadows are observed at the base of the lungs, near the costophrenic sulcus, at the junction of adjoining lobes and near the mediastinum (Fig. 63, p. 582). Pleural effusions are frequent and may conceal the shadow of the infarct itself. There may be a shadow at one base with ultimate elevation of the diaphragm on that side, due to partial atelectasis. Rarely there is localized rarefaction, indicative of necrosis or abscess. Pleural thickening, localized fibrosis or linear shadows may represent scars of old infarcts. According to Westermark[90] and others,[79] pulmonary embolism without infarction may cause transient clearing (avascularity) of the normal shadow of pulmonary tissue distal to the embolism.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of acute cor pulmonale involves (a) the diagnosis of pulmonary embolism plus (b) the diagnosis of right ventricular strain.

Pulmonary embolism should be considered whenever there is a sudden onset of collapse, precordial oppression or chest pain, dyspnea, tachypnea or cyanosis, especially in patients who have been confined to bed for one to three weeks by an operation, fracture, delivery or a medical illness. Often, however, there may be only a clinical picture of shock or sudden weakness with little or no cyanosis, chest pain or dyspnea. Unexplained elevations in temperature and tachycardia in the second week postoperatively are often indicative of pulmonary embolism. In cases of heart failure, unexplained fever, lack of response to therapy, or pleural effusions which are exudates or hemorrhagic should suggest the possibility of pulmonary embolism. Tenderness of the calf muscles, a positive Homans' sign,[44] thickening and infiltration of the deep calf muscles,[65] swelling of the leg and prominence of the superficial veins due to phlebothrombosis of the deep veins of the leg confirm the diagnosis. Often, however, there are neither symptoms nor signs of venous thrombosis. In such cases venography with the aid of contrast media may disclose evidence of venous occlusion.[8, 83, 24]

If death does not occur within twenty-four hours, the diagnosis may be further suggested or confirmed within the next few days by the development of cough and hemoptysis, localized pain on deep breathing, local signs of pulmonary congestion or consolidation, a pleural rub, physical signs of pleural effusion, or by roentgenologic evidences of pulmonary infarction. But none of these may be present if infarction does not result from the pulmonary embolus. The occurrence postoperatively or even in healthy ambulant patients[41, 44, 42] of a peculiar pneumonia or pleurisy should suggest pulmonary embolism as one of the conditions to be considered in differential diagnosis.

The electrocardiogram may disclose distinctive features in about 10 to 20 per cent of pulmonary emboli but in a much higher percentage of massive emboli if the record is taken on the day of the attack (p. 877).

Once a diagnosis of pulmonary embolism is made, the additional diagnosis of acute cor pulmonale depends on the finding of clinical evidence of pulmonary hypertension (e.g., accentuation of P_2, percutory signs of a dilated pulmonary artery), roentgenologic evidence of pulmonary, right ventricular and perhaps right atrial dilatation, electrocardiographic evidence of right ventricular strain

and clinical evidences of acute congestive right ventricular failure (e.g., engorged cervical veins).

The chief problems in *differential diagnosis* concern the distinctions between pulmonary embolism and pneumonia, pleurisy, angina pectoris, coronary occlusion and postoperative shock. Occasionally neurologic manifestations lead to a diagnosis of a cerebral accident. Acute abdominal complications may be simulated when pulmonary infarction is associated with pleural pain referred to the abdomen, and with concomitant nausea and vomiting.

Difficulties in differentiating pulmonary embolism and coronary occlusion are due not only to similarities in the clinical picture but also to the occurrence of coronary occlusion postoperatively and to the frequency with which pulmonary embolism complicates acute coronary occlusion.[39] I have often seen pulmonary embolization following myocardial infarction interpreted as repeated attacks of coronary occlusion.

Among the distinguishing features between acute coronary occlusion and pulmonary embolism is the infrequency of myocardial infarction in females, unless there is diabetes or hypertension;[3] pulmonary embolism occurs with almost equal frequency in both sexes. Hemoptysis is often absent in cases of pulmonary embolism, but when present it is an important distinguishing feature. However, the differential diagnosis usually depends on a consideration of all the clinical features, and especially of the electrocardiogram.

As a rule, acute coronary occlusion is associated with characteristic electrocardiographic abnormalities and distinctive serial changes (p. 442). Furthermore these changes persist much longer than the relatively transient abnormalities associated with pulmonary embolism. Infarction of the posterior ventricular wall causes somewhat similar electrocardiographic changes, but the deep S_1 and the inversion of the T waves in precordial leads V_1, V_2 and V_3 seen after pulmonary embolism do not occur with the former condition.

PROGNOSIS OF ACUTE COR PULMONALE

The outlook after a massive pulmonary embolus is extremely unfavorable. When the embolus is of sufficient size to cause shock or acute right ventricular dilatation, death occurs in the majority of cases. Of 100 clinical cases of pulmonary embolism reported by Takats, Beck and Fenn,[85] 87 died and 13 survived. Similarly Hampton and Wharton[43] report the survival of 10 per cent of patients with pulmonary embolism following gynecologic operations. Pulmonary embolism is regarded as being responsible for about 6 to 10 per cent of all postoperative deaths.[11, 7, 21]

Pulmonary emboli of secondary or smaller branches are usually survived but are often of ominous significance. They are frequently precursors of recurrent embolization which may be terminated by a final massive embolus of the main pulmonary artery or its primary divisions. In 24.4 per cent of 897 cases of pulmonary embolism studied by Barker et al.,[6] the first attack was fatal. But of 343 fatal cases of embolism, the fatal embolism was preceded by one or more nonfatal emboli in 36.2 per cent. These observers noted that if a patient has a nonfatal postoperative pulmonary embolus he has slightly less than one chance in five of subsequent fatal pulmonary embolism, and about three chances in ten of subsequent embolism, fatal or nonfatal. The clinical signs and symptoms of small pulmonary emboli usually subside in a week or two but the clinical course may be prolonged by pleural effusion or suppuration of an infarct.

Even pulmonary emboli of the primary pulmonary arteries may not cause death but may undergo organization and recanalization. Such large emboli or multiple smaller emboli may occasionally produce pulmonary hypertension, right ventricular hypertrophy and failure (chronic pulmonary heart disease or chronic cor pulmonale) (Chapter 39).

TREATMENT OF PULMONARY EMBOLISM

Prophylaxis

Avoidance of Venous Thrombosis. The treatment of massive pulmonary embolism and its cardiac and circulatory sequelae properly begins with prophylaxis against the development and dissemination of venous thrombi.[66] In medical cases it seems desirable to avoid prolonged periods of bed rest unless essential and to avoid immobilization of the body or extremities if bed rest is necessary. Fortunately, the dangers of bed rest, especially pulmonary embolism, have recently been publicized. Since cardiac failure appears to be a frequent predisposing cause among medical cases, adequate treatment of this condition is important.

In surgical cases, care should be exercised in the handling of tissues, and injury or compression of veins draining the lower extremities should be avoided. The position of the patient on the operating table should cause no unnecessary interference with the venous return. Abdominal strappings or binders should not be so tight that they prevent deep breathing. Postoperatively, abdominal distention should be avoided or treated promptly. Motion of the body should be encouraged, and regular frequent exercises of the legs and respiratory exercises should be ordered. Adequate hydration, prompt control of infection and avoidance of chilling are also believed to be valuable prophylactic measures.[7, 69] Reduction of the period of rest in bed may be of major importance in avoiding venous thrombosis.[29] The Trendelenburg position has been recommended to avoid venous thrombosis but Frykholm[31] has opposed its use and advocated elevation of the head of the bed for one to two hours daily in order to distend the collapsed veins in the lower extremities and to compel active movements of the adductor muscles of the thigh.

The routine use of anticoagulants[64] has been recommended following operations, injuries or other conditions requiring complete bed rest, but it is usually difficult and impractical. Anticoagulants are discussed below.

Recognition and Treatment of Venous Thrombosis. Daily examination of the legs for local tenderness over the deep veins, for pain on dorsiflexion of the foot with the leg extended (Homans' sign[44]), and for edema and dilatation of the superficial veins and careful measurement of their circumference to discover swelling, should be performed postoperatively and whenever there is a probability of venous thrombosis. Sudden sharp chest pain, faintness, hemoptysis, fever, tachycardia, dyspnea or other manifestations of pulmonary embolism are usually the first indications of an underlying phlebothrombosis, which is then discovered by local examination.

The treatment of venous thrombosis (phlebothrombosis) to avoid initial or recurrent pulmonary embolism consists essentially of two measures: (1) anticoagulant therapy and (2) thrombectomy and venous ligation.

Anticoagulants. Heparin and Dicumarol. Anticoagulants have been administered for the purpose of preventing venous thrombosis, extension of a thrombus

already formed or enlargement of a pulmonary embolic clot by local thrombus formation. Extremely promising results in the prevention and treatment of phlebothrombosis of the legs and in the prevention of pulmonary embolism have been credited to the use of both heparin[20, 9, 49] and Dicumarol.[15, 2, 27] In a series of 280 cases of postoperative venous thrombosis treated with Dicumarol, there were only 8 instances of further venous thrombosis and none of fatal pulmonary embolism, whereas 68 cases of thrombosis and 16 of fatal embolism might have been expected on the basis of a previous series of venous thrombosis in which Dicumarol was not given.[2]

The anticoagulant action of heparin appears to be due to the inhibition of the conversion of prothrombin to thrombin and impairment of the clotting effect of thrombin on fibrinogen. Dicumarol retards intravascular clotting by decreasing the prothrombin concentration of the blood. Heparin possesses the advantages of prompt effect and rapid cessation of this effect when it is discontinued. On the other hand it is very expensive and must be given parenterally. Dicumarol is extremely inexpensive and is given orally; but it has the disadvantages of a twenty-four to forty-eight hour delay in its anticoagulant effect, persistence of this effect several days after it is discontinued, and the need for special laboratory facilities and skill to control its administration by determinations of the prothrombin time. Both anticoagulants occasionally cause minor bleeding or even fatal hemorrhage.[25a] They are contraindicated in patients with jaundice, hepatic, renal or hemorrhagic disease, and in patients with impaired blood clotting or prolonged prothrombin time. Some believe that they should not be used in surgery of the brain, thyroid or prostate, in cases of subacute bacterial endocarditis or in the presence of ulcerative lesions. If bleeding results from heparin, protamine may be administered intravenously[50, 71] and transfusions given if there is considerable loss of blood. Bleeding due to excessive Dicumarol should be treated by the intravenous administration of 64 mg. of menadione bisulfite (synthetic vitamin K) at four- to six-hour intervals, and if necessary by transfusions with freshly drawn citrated blood.

Heparin dosage is the quantity required to prolong the clotting time to between fifteen and twenty minutes. The clotting time must be checked hourly if heparin is given soon after operation, then every four hours and then daily when the clotting time is fairly stabilized. About 300 mg. of heparin is given daily. It may be administered in a slow continuous intravenous infusion of 5 per cent glucose or physiologic saline, containing 100 to 200 mg. (10 to 20 cc.) of heparin per liter. It has also been administered by intermittent intravenous injections in 50 mg. doses every four to six hours. Stats and Neuhof[84] reported satisfactory results with a concentrated aqueous solution of heparin which was administered intramuscularly in 100 mg. doses every eight hours. Incorporation of heparin in a menstruum of gelatin, dextrose, acetic acid and distilled water has served to prolong its action when administered into the deep subcutaneous tissue of the thigh.[57] After an initial dose of 300 to 400 mg., 100 to 150 mg. of heparin is given every second or third day according to the coagulation time, which is determined daily.

Dicumarol dosage is such that the prothrombin concentration is between 10 and 30 per cent of normal.* The prothrombin time is determined by the method of Quick[73] or some modification. A dilution curve should be made on a normal control indicating the percentage of prothrombin corresponding to various prothrombin times. The patient's prothrombin time, determined with

* This corresponds to a prothrombin time of 25 to 45 seconds when the control is 14 to 16 seconds.

the same batch of thromboplastin as used for the normal control, is then converted into a prothrombin percentage, according to this curve. If heparin is also being given, the prothrombin time should be determined four hours after the last dose.

Usually 300 mg. of Dicumarol is given on the first day, 200 mg. on the second, and thereafter 200 mg. on days when the prothrombin concentration exceeds 20 per cent. No Dicumarol is given on days on which the concentration is 20 per cent or has dropped rapidly. When Dicumarol is administered for venous thrombosis or pulmonary embolism, it is continued for seven days after the patient is ambulant. For rapid anticoagulant therapy heparin is given at the same time as Dicumarol and discontinued after twenty-four to forty-eight hours, when a satisfactory Dicumarol effect has been obtained.

Venous Ligation and Thrombectomy. There have been a number of favorable reports on the effectiveness of ligation of the femoral vein in the prevention and treatment of deep venous thrombosis and in the prevention of pulmonary emboli.[24, 5, 87, 4, 1] There is insufficient comparative data to permit evaluation of the relative merits of anticoagulants and venous ligation or of the specific indications for one or the other method of treatment. Allen and his associates[1] at the Massachusetts General Hospital have recommended only routine prophylactic measures postoperatively, such as early ambulation, leg exercises, etc., in patients below the age of forty and dicumarol therapy in patients between forty and sixty-five if skillful laboratory control of the prothrombin level is available. In patients beyond the age of sixty-five and in selected "prematurely old or debilitated persons" in whom postoperative thrombosis is especially common, they recommend prophylactic bilateral ligation of the superficial femoral veins.

Once phlebothrombosis or pulmonary embolism occurs, they advocate the opening of these veins and removal of the thrombus with the aid of suction. This is followed by ligation of the vein in its upper 2 cm., as close to the junction with the profunda femoris as possible. Anticoagulants are administered only if thrombophlebitis or pulmonary embolism occurs after the venous ligation. There is disagreement among other surgeons as to the need for bilateral ligation when there are distinct signs of thrombosis confined to one leg. Some surgeons prefer to ligate a normal segment of vein above the clot; this often necessitates ligation of the common femoral or common iliac veins, which may be followed by evidences of chronic venous insufficiency. Interruption of the inferior vena cava[32, 70] may be necessary if there are recurrent septic pulmonary infarcts or if it appears probable that the thrombi are situated in the iliac or pelvic veins.

Treatment of Pulmonary Embolus

The direct treatment of the pulmonary embolus itself aside from the use of anticoagulants is unsatisfactory. Based on the experimental observations which indicate the occurrence of vagal reflexes with spasm of the coronary vessels and other smooth muscle structures, *atropine* has been administered *intravenously* in repeated doses of 0.6 mg. (1/100 grain), and *papaverine hydrochloride* by the same route in doses of 0.03 gm. (½ grain). With massive embolization the latter may be repeated at hourly intervals. Morphine or demerol may be necessary for pain and restlessness.

Oxygen should be administered, in cases of massive pulmonary embolism, by nasal catheter, mask or tent, or in 100 per cent concentration by the special

mask of Boothby and his associates.[13] Venesection is contraindicated, despite the elevated cervical venous pressure, since the latter is a necessary compensatory mechanism and the effective circulatory volume is low.

Surgical removal of an embolus in the main pulmonary artery or its bifurcation (Trendelenburg operation) has been successfully performed and strongly advocated by Kirschner[52] and Meyer.[61] This requires a well trained organization which may be rapidly set into action when the diagnosis is made. The procedure can be utilized for those patients who survive for more than an hour. According to Takats, Beck and Fenn,[85] the Trendelenburg operation was carried out 132 times with a mortality of 93.2 per cent, but these operations were performed almost exclusively on rapidly fatal cases.

FAT EMBOLISM

Embolism of the pulmonary circulation may result from the entrance of free globules of fat into the systemic veins.[100, 99, 102, 104] In some cases the clinical picture does not differ significantly from that of acute cor pulmonale.

The most common cause of fat embolism is a fracture of a long bone, especially the femur, tibia or both.[105, 104] Occasionally orthopedic procedures, blast injuries or other forms of trauma to bone marrow or subcutaneous adipose tissue, osteomyelitis, various poisons or burns may also produce fat embolism.[103] In addition to the mobilization of fat, the disruption of veins which remain patent and local pressure are factors contributing to fat embolism. Recently fat embolism has been reported following the therapeutic intravenous administration of ether.[96]

The fat which is released from its intracellular structure reaches the right side of the heart and the pulmonary arteries by way of the systemic veins. Occasionally a large amount of liquid fat may obstruct the main pulmonary artery[98] and thus sharply reduce the cardiac output and cause acute right ventricular dilatation. More frequently the fat globules reach the pulmonary capillaries, where they may be trapped and where they may cause widespread pulmonary obstruction with lesions in the affected lung tissue. As a rule, some of the globules of fat traverse the pulmonary capillaries and reach the systemic (arterial) circulation, where they block the capillaries and arterioles of the brain, the skin, heart and numerous internal organs. Fat emboli may also reach the systemic circulation from the right side of the heart by way of a patent foramen ovale. The occurrence of clinically significant coronary occlusion due to fat embolism is unproven.[94]

The *clinical features* are determined chiefly by embolic lesions in the lungs and the brain. Characteristically, after an injury the patient has a free interval of relative comfort lasting from six hours to two or three days. If there is a massive occlusion of the pulmonary artery by a large quantity of liquid fat, death may occur suddenly with a clinical picture of shock, air hunger and pulmonary edema. More commonly, a few days after the injury the patient begins to suffer from dyspnea and restlessness, followed by sweating, pallor or cyanosis, and cough with blood-tinged sputum. Tachycardia, tachypnea and fever are frequent. There are often diffuse moist râles and other signs resembling those of pulmonary consolidation or edema. Free fat droplets may be demonstrated occasionally in the sputum by staining with Sudan III, but it is doubtful whether this is pathognomonic of pulmonary fat embolism. Roentgenograms of the chest may reveal bilateral patchy pneumonic consolidation.[101]

Cerebral symptoms may be combined with or follow these pulmonary manifestations. More often they appear several hours to days after the injury without preceding pulmonary symptoms. The patient suffers from somnolence, disorientation or delirium. There may be convulsions, paralyses, loss of sphincteric control, and stertorous or Cheyne-Stokes respiration. Fat emboli in the retinal arteries have been visualized opthalmoscopically.[95] Occasionally fever, stupor and coma are the essential signs of fat embolism without preliminary pulmonary or localizing cerebral signs. The occurrence of dark red petechial hemorrhages on the skin of the anterior chest, arms and neck is of diagnostic value.

Recovery may occur,[95, 93] probably independently of the treatment employed. In fatal cases death usually occurs after two or three days. The avoidance of further trauma in handling and transporting injured patients is emphasized in the prophylaxis of fat embolism. Treatment is symptomatic. Oxygen therapy is administered if there is cyanosis and dyspnea. Epinephrine or ephedrine has been recommended. Sodium desoxycholate (10 cc. of 20 per cent solution by slow intravenous drip every two hours) has been suggested as a therapeutic measure by Rappert,[97] with the object of emulsifying the fat globules and thus reducing the elevated blood viscosity.

AIR EMBOLISM

When air rapidly enters the systemic veins in large quantities, it reaches the right ventricle, where, because of its easy compressibility, it interferes with ventricular contraction.[115] Air embolism may also obstruct the main stem of the pulmonary artery.[118] It may also produce pulmonary obstruction by causing widespread embolization of the pulmonary arterioles or capillaries.[112, 116] According to Curtillet,[107] air bubbles do not reach vessels less than 30 micra in diameter and therefore they are arrested in the arterioles. The presence of air in the ventricular cavity may be revealed by a loud churning or waterwheel murmur over the precordium. Death often results suddenly with or without premonitory cyanosis or pallor, evidences of shock, dyspnea and stertorous respiration and coma. These manifestations result from diminished cardiac output, pulmonary anoxemia and eventually cerebral anoxemia.

While *systemic venous air embolism* occurs mostly in the course of major surgical operations on the thyroid gland and other structures of the neck where the veins are large and kept widely patent by fascial structure, it may also complicate numerous minor diagnostic and therapeutic procedures. These include among others tubal insufflation and urethroscopy, perirenal insufflation, irrigation of the nasal sinuses, pneumoperitoneum, direct transfusions, and uterine douches or adoption of the knee-chest position in the puerperium. In recent years, air embolism has been noted after criminal abortions and vaginal powder insufflations.[113]

According to experimental studies, smaller quantities of air are required to cause death when injected into a pulmonic vein than when injected into a systemic vein.[114] When air enters the pulmonary vein, it reaches the left side of the heart and systemic arterial circulation. Such arterial air emboli may also occur when air is introduced into a systemic vein, if there is an interauricular communication. As a rule, air emboli reaching the pulmonary arterioles from a systemic vein do not cross to the pulmonary vein and systemic arterial circulation, as do fat emboli.[107] Arterial air emboli cause serious symptoms chiefly by occluding arterioles or capillaries of the brain. Air emboli also involve the

coronary arteries at the same time.[114] Durant[108] reported a case of air embolism in which there were characteristic electrocardiographic changes such as occur after a cardiac infarction. By means of roentgenography Balogh[106] noted a reflux of air from the right ventricle into the thebesian and coronary veins. He believed that this causes coronary stasis and may be responsible for clinical symptoms.

Clinically, *systemic arterial air embolism* results most often from the entrance of air into the pulmonic veins in the course of pleuropulmonary operations or artificial pneumothorax.[111] It also occurs after chest injuries and pleural lavage of empyema cavities. So-called pleural shock may in reality represent air embolism. Symptoms appear rapidly, beginning with dizziness or pallor and followed by mental confusion, disorientation, hallucinations, convulsions, vomiting, paralyses, especially hemiplegia or monoplegia, and amaurosis. The latter is due to air embolism of the retinal arteries which sometimes may be visualized clinically with the ophthalmoscope.[117] Marbling of the skin may result from obstruction of the cutaneous vessels or from shock. Coma and death may occur within fifteen minutes. Patients surviving an hour or longer usually recover. Blindness and paralyses disappear in most cases, but there may be residua.

Therapy is unsatisfactory. Maintenance or assumption of the head-down position is recommended to avoid floating of the air bubbles into the cerebral vessels. The Trendelenburg position is desirable at operations in which air embolism may be anticipated (e.g., chronic pulmonary abscess). In the experimental animal with systemic venous emboli (to the right ventricle), displacement of the air trap by turning the body into the left lateral position may be lifesaving.[109] Inhalation of 100 per cent oxygen has been recommended on the basis of experimental studies.[110]

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CHRONIC PULMONARY HEART DISEASE— CHRONIC COR PULMONALE

DEFINITIONS

Pulmonary heart disease and *cor pulmonale* are terms applied to the hypertrophy of the right ventricle, with or without congestive heart failure, resulting from disease of the lungs or pulmonary vascular tree. In recent years the adjective chronic has been added to distinguish cor pulmonale secondary to chronic pulmonary affections from the acute cor pulmonale resulting from massive pulmonary embolism.

Ayerza's "Disease" or Syndrome

The term Ayerza's disease[94] or Ayerza's syndrome refers to a clinical syndrome characterized by intense cyanosis, polycythemia and congestive heart failure, usually associated with bronchopulmonary symptoms but without primary cardiac disease. Ayerza had referred to the syndrome as *cardiacos negros* (black cardiacs),[5] because of the deep cyanosis of the affected patients. At present there are multiple concepts of the etiology of Ayerza's syndrome, even among Ayerza's students. One theory attributes it to syphilitic pulmonary arteritis,[4, 31] another to bronchial syphilis and pulmonary arteriosclerosis,[45] another to primary nonsyphilitic sclerosis of the pulmonary artery, and still another to various bronchopulmonary diseases with or without secondary pulmonary atherosclerosis.[26] Ayerza's[5] syndrome applies merely to those cases of nonvalvular chronic pulmonary heart disease in which there are intense purple cyanosis, polycythemia and eventually evidences of congestive heart failure.

Hypertension of the Pulmonary Circulation

Despite a varied etiology of chronic cor pulmonale, it is generally assumed that there is probably a unitary mechanism producing it, namely, an increased resistance and therefore an increased pressure in the pulmonary circuit. Measurements of the right ventricular pressure by intracardiac catheterization have disclosed an elevation of the systolic and pulse pressures, but the diastolic ventricular pressure was normal in the absence of heart failure.[16] The occurrence of exclusive or predominant right ventricular hypertrophy is indirect evidence of increased pulmonary resistance to ventricular outflow. The increased

frequency and extent of pulmonary arteriosclerosis in cases of chronic cor pulmonale has also been interpreted as resulting from and denoting the presence of pulmonary hypertension.[90, 102]

Etiology of Pulmonary Hypertension and Chronic Cor Pulmonale. Pulmonary hypertension may be caused by a variety of pulmonary, cardiac and vascular disturbances which fall into three broad groups:

1. Mitral stenosis and, less commonly, other causes of left-sided heart failure which result in pulmonary congestion.

2. Extensive disease of the lungs or pulmonary arteries which greatly increases the resistance in the pulmonary circulation. Obstruction of the pulmonary artery from without by a compressing aortic aneurysm or tumor may produce a similar effect.[130]

3. Congenital cardiac lesions with an arteriovenous shunt, such as a patent ductus arteriosus, septal defects, or pulmonary veins entering the right atrium or superior vena cava. An acquired aortic-pulmonary shunt caused by rupture of a syphilitic aortic aneurysm into the pulmonary artery may produce dynamic disturbances similar to those of a patent ductus arteriosus.

The term chronic cor pulmonale or chronic pulmonary heart disease as used in this chapter and elsewhere in this book is confined only to the second group, in which strain of the right heart is caused by primary disease of the lungs or pulmonary vessels. The acute form of cor pulmonale due to massive pulmonary embolism was discussed in the preceding chapter.

Among the chronic pulmonary diseases responsible for heart disease are emphysema, asthma, pulmonary tuberculosis, pneumoconiosis, kyphoscoliosis and other chest deformities, and various diseases of the pulmonary arteries. Chronic cor pulmonale due to emphysema will be discussed in some detail and the remaining etiologic diseases only with respect to special points.

COR PULMONALE DUE TO PULMONARY EMPHYSEMA (EMPHYSEMA HEART)

Pulmonary emphysema is the classic cause of cor pulmonale. The terms cor pulmonale and emphysema heart were long used interchangeably, although the former has come to embrace cases of right ventricular hypertrophy due to many other pulmonary lesions besides emphysema.

Incidence

Studies based on autopsy material are more likely to disclose heart disease due to emphysema than those based on clinical cases, because of the long life history of pulmonary emphysema and the late appearance of cardiac manifestations. Thus Parkinson and Hoyle,[109] in their excellent clinical report of 80 cases of pulmonary emphysema, concluded that cardiac signs and evidences of cardiac failure were rarely due to that disease and were usually caused by associated cardiac disease, especially hypertension. On the other hand, in recent reports of necropsied cases of pulmonary emphysema, Griggs and his associates[57] noted right ventricular hypertrophy in 28.9 per cent and congestive heart failure in 22.3 per cent of 45 uncomplicated cases; Parker[108] observed hypertrophy of the right ventricle in 75 per cent and cardiac failure in 44 per cent of 32 cases; Scott and Garvin[130] found cor pulmonale due to emphysema in 50 (6.3 per cent) of 790 autopsied patients who had died of heart disease.

Pathology

The Lungs. Forms of Emphysema. Three forms of chronic vesicular emphysema have been described: (1) *Vicarious or compensatory emphysema,* in which normal pulmonary alveoli become distended to compensate for diseased or collapsed alveoli in other parts of the lung. (2) *Senile, atrophic or nonobstructive* emphysema, observed usually in elderly subjects with kyphosis, and due either to atrophy of the elastic and fibrous tissue of the alveolar septa with consequent rupture, or to degeneration and atrophy of the intervertebral disks.[79] Senile emphysema does not produce any cardiac or circulatory symptoms. (3) *Obstructive or hypertrophic emphysema*[80] is the form which is responsible for emphysema heart, although compensatory emphysema may also contribute to the development of cor pulmonale. The lungs in cases of obstructive emphysema are large, appear in a position of deep inspiration, and, because of a loss of elasticity, do not collapse when the chest wall is opened. *Microscopically,* the alveolar spaces appear enlarged and in many places confluent, with the septa ruptured, incomplete, atrophic or missing entirely. Although the size of the lungs as a whole is increased, the surface area of the alveolar septa, where hemorespiratory exchange occurs, may be greatly diminished.

Various theories of the pathogenesis of obstructive emphysema have been proposed.[134, 89] The essential cause of this form of emphysema is an obstruction to the passage of air through the bronchial tubes due to inflammatory changes in the bronchial walls, bronchial exudate and bronchospasm.[72] Distention of alveoli and loss of pulmonary elasticity result from the consequent forced inspiration[114] and perhaps also in cases of chronic cough from forced expiration. A constitutional deficiency of the pulmonary elastica may be a contributing factor.

The Pulmonary Vessels. The essential abnormalities concern the capillary bed. The changes in the alveolar septa result in fibrosis, narrowing, thrombosis or complete obliteration of capillaries.[70] In consequence, there is a marked reduction in the total cross-sectional area of the available capillary circulation.

Arteriosclerotic changes in the larger pulmonary arteries as well as in the small arteries and arterioles of patients with advanced emphysema are more frequent and more severe than is usual for normal patients of similar age.[136, 99, 103, 21] The pathogenesis of these arterial lesions is still disputed, but most investigators believe that they are secondary to the pulmonary hypertension resulting from the pulmonary emphysema.[102, 122] Arteriosclerosis of the smaller pulmonary arteries may narrow the lumens sufficiently to add significantly to the increased pulmonary resistance due to the capillary disturbance.[108]

The Heart. The characteristic feature of cor pulmonale is hypertrophy of the right ventricle. A variable degree of right ventricular dilatation is also present, but this is more difficult to evaluate. In cases with right-sided heart failure there is usually also dilatation and occasionally hypertrophy of the right atrium.

Right ventricular hypertrophy in cases of pulmonary emphysema has been demonstrated by weighing the chambers separately according to the method of Müller.[65, 77] By means of linear measurements of the extent of the chambers, Kirch[77] found that the hypertrophy began in the outflow tract of the right ventricle (p. 25), i.e., the anterior half of the chamber extending from the apex to the pulmonary arteries. Right ventricular hypertrophy eventually develops in 25 to 75 per cent of cases of pulmonary emphysema.[21, 81, 57, 108] For sim-

plicity many observers have assumed that the right ventricle is enlarged if its average thickness exceeds 5 mm. Right ventricular hypertrophy may be overlooked if this chamber is not separately weighed or measured because the weight of the heart as a whole may not be significantly increased.

A remarkable observation is the frequent presence of associated left ventricular hypertrophy in autopsied cases of pulmonary emphysema, in which hypertension, aortic valvular disease and other possible causes of such hypertrophy have been reasonably excluded.[81, 108] But hypertrophy of the left ventricle occurs less often and is less pronounced than that of the right ventricle. The cause of left ventricular hypertrophy in pulmonary emphysema is uncertain. The frequency of granular and contracted kidneys (in 22 out of 33 cases of pulmonary emphysema) noted by Gull and Sutton[59] in 1872 suggests that there was a high incidence of hypertension in these cases. Similarly unrecognized or antecedent hypertension may be responsible for the left ventricular hypertrophy in more recently reported cases of pulmonary emphysema. Arterial anoxemia may also be a contributory causative factor.

Pathologic Physiology

The pulmonary changes in cases of obstructive emphysema may lead to four essential functional disturbances: (1) impaired pulmonary ventilation, (2) impaired aeration of the blood, (3) increased cardiac output and (4) right ventricular strain.

1. Impaired Pulmonary Ventilation. There is a loss of pulmonary elasticity and a consequent reduction in the retractile power of the lung. Therefore even after expiration, the lungs are in an inspiratory position with the diaphragm low; the inspiratory expansion of the lungs is minimized. Further respiratory inefficiency is due to uneven expansion of the rigid lung, unequal distribution of the inspired air,[118] dilution of the inspired air by an excessive volume of residual air in the lungs after expiration, and bronchial obstruction by inflammatory exudate and spasm.

Respiratory measurements[32, 82, 68] reveal a reduction in the excursion of negative intrapleural pressure during respiration, a tendency to loss of negative intrapleural pressure denoting pulmonary rigidity, a pronounced *increase in residual air* with a slight increase in total pulmonary capacity and a *reduction in vital capacity*. This contrasts with the findings in pulmonary congestion due to left heart failure in which the residual air and total capacity are usually diminished. The *minute volume* is *increased* due chiefly to an increase in tidal volume (volume of each ordinary respiration). Despite the increased minute volume of respiration the oxygen consumption is normal, i.e., respiratory efficiency is diminished because respiratory work is increased in order to maintain a normal oxygen consumption. There is also a reduction in the maximal breathing capacity as determined by having the patient breathe in and out as fast and deeply as possible for 10 to 20 seconds. (Normal = 100 to 150 liters per minute.) The increased actual ventilation and the diminished maximal breathing capacity result in a reduction in the *respiratory reserve* (the difference between the former two values). The patient with pulmonary disease usually experiences dyspnea when his breathing reserve is less than 70 per cent of his maximal breathing capacity.

2. Impaired Aeration of the Blood. Impaired aeration of the blood flowing through the pulmonary alveoli results not only from subnormal alveolar oxygen

tension due to deficient pulmonary ventilation but also from a reduction in the capillary bed. This is due to atrophy and disappearance of the alveolar septa and their capillaries in emphysema. Aeration is also impaired by the inefficient distribution of tidal air chiefly to the distended peripheral alveoli which have the poorest blood supply.[32, 118]

The increased minute volume of respiration compensates for the inefficiency in ventilation and impaired aeration of the blood, but reduces the respiratory reserve. With the enhanced metabolic demands of exercise, further respiratory increase of the rigid lungs is limited or impossible and normal aeration of the blood cannot be maintained. With more advanced pulmonary emphysema the arterial oxygen of the blood is reduced significantly even when the patient is at rest.[69, 97] The effective pulmonary blood flow, i.e., the percentage of pulmonary capillary blood which is oxygenated, was found to average 69 per cent in a group of patients with severe pulmonary emphysema.[116a]

Because of the greater diffusibility of carbon dioxide, the hyperventilation in pulmonary emphysema more readily eliminates excessive carbon dioxide than it maintains adequate oxygenation. Therefore a retention in carbon dioxide occurs less frequently and later than a reduction in arterial oxygen.[69] But when the ratio of residual air to total capacity exceeds 45 per cent, both carbon dioxide retention and arterial anoxemia develop.[68] The pH of the blood is rarely altered except terminally, for there is a compensatory increase in the alkali reserve as indicated by the elevation in carbon dioxide.

3. Increased Cardiac Output. When increased minute volume of respiration no longer compensates sufficiently to maintain a normal oxygen content of the arterial blood, other compensatory mechanisms serve to provide the tissues with an adequate supply of oxygen.[138] As in cases of anemia, this is accomplished by an increased cardiac output (minute volume blood flow[97]). In advanced pulmonary emphysema with considerable arterial oxygen unsaturation, the speed of the circulation is increased[50] and the venous return thereby augmented. This in turn is translated into the greater cardiac output.

Another compensatory mechanism is the development of polycythemia, probably in response to the anoxemic stimulus of the bone marrow.[85, 144] The erythrocytosis tends to restore the normal *content* of oxygen despite the diminution in percentage of oxygen saturation.

When the heart fails, the cardiac output falls although it may still exceed the usual normal range. The high output is not sufficiently high to supply the needs of the tissue against the handicap of arterial anoxemia. When a severe bronchopulmonary infection complicates advanced pulmonary emphysema, the above compensations are inadequate to maintain tissue oxygenation, not because of heart failure, but because the impairment of pulmonary aeration is too extreme (pulmonary failure).

4. Right Ventricular Strain. The functional disturbances in respiration and aeration of the blood as well as the compensations of increased volume of ventilation, increased cardiac output and erythremia may all occur in uncomplicated pulmonary emphysema. Pulmonary heart disease or cor pulmonale may be said to be present only when there is evidence of right ventricular strain, as indicated by hypertrophy of the right ventricle, or evidence of pure right ventricular failure.

Right ventricular strain is due to an increase in pulmonary resistance which tends to cause incomplete right ventricular emptying and a diminution in stroke

output. The increased pulmonary vascular resistance has been attributed to (a) a striking reduction in the capillary bed,[24] (b) narrowing of the vessels by increased intraalveolar tension and (c) secondary pulmonary arteriolosclerosis. Compensatory dilatation and subsequent hypertrophy restore the stroke output despite the elevation in pulmonary resistance.[47] The increase in pulmonary resistance and the consequent right ventricular strain are rarely as great as that caused by mitral stenosis or other lesions associated with left-sided heart failure and pulmonary congestion. For this reason eventual right-heart failure occurs less frequently and later in pulmonary heart disease than in cases of right ventricular strain secondary to left heart failure. During the compensated phase, measurements by intracardiac catheterization have shown an elevation in right ventricular and pulmonary arterial pressure. When right heart failure occurs, the right ventricular diastolic and the right atrial pressure also rise. In most normal individuals, the mean pulmonary arterial pressure falls during exercise and the pulmonary vascular resistance diminishes. In patients with chronic pulmonary disease during exercise there is a significant elevation in mean pulmonary arterial pressure and no change or an increase in pulmonary vascular resistance.[64, 116]

The coronary arteriosclerosis which complicates essential (systemic) hypertension and causes left ventricular failure is less important in cases of pulmonary hypertension, because the right ventricle rarely suffers serious damage from coronary arteriosclerosis. On the other hand, the high pressure in the right ventricle in cases of pulmonary heart disease, by interfering with coronary drainage into that chamber, may impair the blood supply to the hypertrophied right ventricle and accelerate heart failure.[142] Coronary drainage into the left ventricle by way of the thebesian vessels is relatively insignificant and is not influenced much by a rise in left intraventricular pressure. When pulmonary emphysema is advanced enough to cause severe arterial anoxemia, the latter may contribute to failure of the enlarged right ventricle.

Clinical Features

Three stages should be distinguished in the life history of emphysema: (1) uncomplicated pulmonary emphysema, usually with bronchitis and/or asthma; (2) compensated pulmonary heart disease; (3) decompensated pulmonary heart disease. Pulmonary insufficiency may occur during any one of these stages.

1. *Uncomplicated emphysema* is characterized by dyspnea on exertion and by cough with expectoration. There are often associated spasms of bronchial asthma. Not infrequently there is chest pain and occasionally hemoptysis and weakness. Respirations may be labored even at rest. Cyanosis is usually present but is of slight degree. With pulmonary failure cyanosis may become intense. The veins in the neck are often prominent, but the venous pressure is normal or only slightly elevated. The chest is barrel-shaped, its expansion is slight and respirations are costal. Percussion reveals hyper-resonance, a low position and relative immobility of the diaphragm. The expiratory sounds are prolonged and there may be sonorous or sibilant râles. Cardiac and hepatic dullness is diminished or obliterated and heart sounds are distant. Fluoroscopy reveals a low diaphragm with restricted mobility, unchanging translucency of the pulmonary fields even in expiration, clear definition of the diaphragms even in expiration,[49] and wide intercostal spaces. This stage of uncomplicated emphysema is of long duration, exceeding five years in a majority of cases.

2. *The compensated stage of pulmonary heart disease* is characterized by the addition of signs of pulmonary hypertension and right ventricular enlargement to those of uncomplicated emphysema. As this usually is associated with a more advanced stage of emphysema, exertional dyspnea is more marked and there may be dyspnea at rest. Occasionally in this stage cyanosis is intense and associated with polycythemia, but rarely with clubbing. It is often difficult to distinguish this stage from that of uncomplicated emphysema in which pronounced cyanosis and dyspnea may occur in the absence of cardiac involvements. Pulmonary hypertension may be denoted by accentuation of the second pulmonic sound, and right ventricular hypertrophy by a prominent impulse in the epigastrium.[133] There may be roentgenologic evidence of dilatation of the pulmonary arteries and of the right ventricle (see below). There may be electrocardiographic signs indicative of right ventricular strain (see below). This compensated stage of cor pulmonale may also be one of many years' duration.

3. *The decompensated stage of pulmonary heart disease* is characterized by the addition of evidences of right-sided congestive heart failure to the symptoms and signs already mentioned. Dyspnea and cyanosis are often intensified. Occasionally the cyanosis is so deep that the patient may be properly termed a "black cardiac." Associated with intense cyanosis may be polycythemia and cerebral symptoms such as fainting attacks, vertigo or somnolence, all probably indicating cerebral anoxemia. Rarely attacks of precordial pain have been attributed to myocardial anoxemia associated with increasing cyanosis (hypercyanotic angina—Posselt[113]). Except for hepatic enlargement, systemic venous congestion and peripheral edema, the other manifestations may be entirely due to advanced emphysema with pulmonary failure and therefore independent of cor pulmonale and heart failure.

The superficial veins become definitely engorged and the venous pressure elevated. The liver is enlarged and usually tender. Peripheral edema appears and occasionally ascites. The course of heart failure is of relatively short duration and progressively unfavorable. In the series of cases studied by Scott and Garvin[130] 86 per cent died of their first attack of cardiac failure. In some instances I have seen death from chronic pulmonary emphysema (pulmonary failure) attributed erroneously to congestive heart failure because of a sudden intensification of cyanosis, dyspnea and cough. In these cases the cause of death was an unrecognized, acute terminating bronchopulmonary infection. In other cases, however, such an infection, by increasing the strain on the enlarged right ventricle, may precipitate congestive heart failure.

Circulatory Measurements. The venous pressure in uncomplicated emphysema is usually normal.[145] In severe cases with elevated intrapleural pressure the venous pressure may also be elevated, probably due to the hindrance to venous inflow presented by the rise in intrapleural pressure.[82] An asthmatic attack may further elevate the venous pressure in patients with advanced emphysema, but Oppenheimer and Hitzig[106] observed normal venous pressures during paroxysms of bronchial asthma in patients without cardiac disease. The development of right ventricular enlargement in cases of pulmonary emphysema is not marked by any change in venous pressure, but a distinct rise occurs when the right ventricle fails. Measurements by means of intracardiac catheterization showed normal right atrial and right ventricular diastolic pressures but elevated right ventricular systolic blood pressure in cases of chronic pulmonary emphys-

ema without heart failure. In the presence of heart failure the right atrial and the right ventricular diastolic pressures were also elevated.[16, 10a]

The *circulation time* is normal in uncomplicated pulmonary emphysema,[145, 139] even during an attack of bronchial asthma,[106] and it remains normal during the compensated stage of chronic cor pulmonale. However, when the emphysema is advanced enough to induce intense arterial anoxemia, the circulation time may be significantly reduced, probably due to peripheral vasodilatation as in cases of severe anemia. During the stage of right-sided heart failure there is a prolongation in both the arm-to-tongue (saccharin) time and in the arm-to-lung (ether) time. The difference between these two times, i.e., the lung-to-tongue time, is normal because all of the delay occurs between the systemic veins and the pulmonary capillaries. When there is severe emphysema, the delay in circulation due to heart failure may be neutralized by the acceleration due to pronounced arterial anoxemia.

The *circulating blood volume* may be normal in mild cases of emphysema heart but is increased in severe cases with arterial anoxemia and polycythemia.[111, 141] The increased blood volume is due to the increase in erythrocytes. However, in the presence of heart failure, the plasma volume may also be augmented.

Roentgenology. *Compensated Stage of Cor Pulmonale.* There may be roentgenologic evidences of pulmonary hypertension, i.e., dilatation of the pulmonary artery and its branches, but enlargement of the right ventricle is rarely demonstrable. The recognition of the latter is made difficult by the low diaphragm with consequent median position of the heart and by the barrel-shaped chest which permits such enlargement to occur in an anterior direction, without displacement of the cardiac borders to the left or right. The following roentgenologic alterations in emphysema heart disease have been described[38, 109, 117] (Fig. 11*A*, p. 30).

1. Exaggeration of the hilar shadows, due to the enlargement of the main pulmonary arteries and their chief subdivisions.

2. Prominence or convexity instead of the normal concavity of the left middle (pulmonary) arc.

3. Enlargement of the right ventricle. This may be demonstrable by angiocardiography, which discloses a convexity of the interventricular septum to the left, instead of to the right as in the normal heart.[137] In the lateral view, in which the right ventricle forms the anterior border of the silhouette, there may be encroachment on the retrosternal space.

According to Binhold[15] there is usually an increase in the total volume of the emphysematous heart, as determined by Kahlstorf's method. The left atrium is normal, but the left ventricle may appear slightly enlarged, probably due to independent disease or anoxemia.

Decompensated Stage of Cor Pulmonale. In addition to the above, with the development of heart failure the right atrium may become enlarged, as indicated by an increase in the right lower silhouette and of the entire transverse diameter. The shadow of the superior vena cava may also become wide and prominent. The enlargement of the right ventricle is more noticeable and involves the inflow as well as the outflow tract (p. 30).

Electrocardiogram. The electrocardiogram of chronic cor pulmonale may disclose no abnormality or the following changes due to a vertical position

of the heart, depression of the diaphragm and/or right ventricular strain[130, 109, 93, 149] (Fig. 17, p. 39).

(1) Prominent peaked P waves in leads II and III and V_F, with P_3 higher than P_1 (Fig. 18*B*, p. 42). Negative P wave in V_L. There may be a prominent atrial T wave.

(2) S_1 is usually prominent and R_3 tall. S_1 and Q_3 may be present, denoting clockwise rotation of the heart.

(3) T_3 is often inverted and T_2 may be isoelectric or inverted; T is also inverted in V_F.

(4) In the chest leads: (a) The R wave is small and the S deep in the left precordial leads.
(b) The T and P waves are inverted in the right precordial leads.
(c) There may be a late origin of the R wave in the right precordial leads.

The relative importance of the position of the heart and of hypertrophy and dilatation of the right ventricle in the production of these changes is discussed elsewhere (p. 39).

Diagnosis of Chronic Cor Pulmonale

The diagnosis of chronic cor pulmonale is based on recognition of (1) underlying pulmonary disease and (2) right ventricular enlargement with or without failure, and on (3) exclusion of mitral stenosis and other cardiac causes of right ventricular enlargement.

The history and physical and roentgenologic examination of the chest will usually reveal the presence and nature of the pulmonary disease and exclude primary cardiovalvular disease. It is often difficult to differentiate uncomplicated emphysema from compensated cor pulmonale. The diagnosis of the latter requires demonstration of right ventricular enlargement as indicated by the roentgenologic and electrocardiographic signs.

When evidence of right-sided heart failure is added to that of the primary pulmonary disease, the diagnosis of pulmonary heart disease is more definite. However, dyspnea, cyanosis and even a slight elevation of venous pressure may be due to emphysema alone. Hepatic enlargement and subcutaneous edema in addition to a pronounced elevation in venous pressure and prolongation of circulation time are indicative of right-sided heart failure. Extreme intensification of cyanosis and dyspnea is usually due to pulmonary insufficiency and not to the development of right heart failure.

Prognosis

Uncomplicated obstructive emphysema may last a great many years without leading to either right ventricular strain or failure. Despite the presence of distressing and sometimes disabling symptoms, a normal life span is possible. However, premature death often occurs from complicating respiratory infections, especially bronchopneumonia.

Even when there are roentgenologic and electrocardiographic evidences of right ventricular strain, cardiac failure may never develop and the prognosis is essentially that of pulmonary emphysema. Once congestive heart failure appears, the prognosis is extremely unfavorable. The response to treatment is almost always unsatisfactory. Death usually occurs within six months to a year from the first attack of failure. Of the 50 cases of cor pulmonale due to ob-

structive emphysema, with and without other pulmonary diseases, studied by Scott and Garvin,[130] 43 or 80 per cent died of their first attack of cardiac failure.

Treatment

In the compensated stage of chronic cor pulmonale, treatment is concerned only with the underlying emphysema or other pulmonary disease. Mechanical measures have been recommended to improve respiration by raising the diaphragm and increasing its excursions, e. g., the use of an abdominal binder or belt and various exercises.[79, 28, 8]

Episodes of acute pulmonary failure are usually due to an intercurrent bronchopulmonary infection and are often confused with acute heart failure. The administration of oxygen to improve pulmonary aeration of the blood, and sulfonamides or antibiotics to control infection, are the most important therapeutic measures. These measures are also valuable when heart failure is precipitated by a bronchopulmonary infection. Ephedrine and antihistaminic drugs may be beneficial. Morphine causes serious respiratory depression and occasional fatalities in patients with pulmonary failure and is therefore contraindicated.

When frank right heart failure develops, oxygen therapy, control of infection and the use of ephedrine are the chief therapeutic measures. Thiouracil has been recommended.[66] Digitalis is usually not beneficial but should be given a therapeutic trial. Venesection has been discouraged because the high venous pressure and the associated high output are considered compensatory and therefore should not be lowered. Furthermore the increase in erythrocytes is considered compensatory and its reduction dangerous. I believe these opinions are based in part on a misinterpretation of acute pulmonary failure (with intensification of cyanosis and dyspnea) as representing heart failure. When these manifestations are due to pulmonary and not myocardial insufficiency, venesection is contraindicated. But in the presence of a large congested liver, peripheral edema and a high *plasma* as well as cell volume, venesection should be performed and is beneficial. A reinfusion of packed red cells should be carried out if there is severe arterial anoxemia as well as heart failure.

OTHER CAUSES OF CHRONIC PULMONARY HEART DISEASE

In general, the pathogenesis of cor pulmonale resulting from various other pulmonary diseases and the associated clinical features are similar to those described above for emphysema. Therefore, these diseases will be discussed briefly, and only special points or differences will be noted.

Bronchial Asthma

While bronchial asthma undoubtedly causes cor pulmonale indirectly by first producing severe obstructive emphysema, it is doubtful whether it can do so directly. Right ventricular hypertrophy has been found repeatedly in autopsied cases in which there was associated pulmonary disease but not in uncomplicated cases of asthma.[92, 35, 60, 125]

Pulmonary Tuberculosis

Pulmonary tuberculosis, like obstructive emphysema, may produce both right ventricular hypertrophy and congestive heart failure, provided there is

extensive involvement of the lungs and their vascular bed.[57, 77, 1] According to Griggs, Coggin and Evans,[57] pulmonary tuberculosis was associated with right ventricular hypertrophy in 3.7 per cent and congestive heart failure in 1.8 per cent of 1470 cases, but a higher incidence was noted in the smaller series of Ackerman and Kasuga.[1] The right ventricular hypertrophy is attributed to increased pulmonary vascular resistance secondary to narrowing of the arteriolar and capillary bed by extensive fibrotic lesions.[30]

While Nemet and Rosenblatt[104] found electrocardiographic evidence of right ventricular preponderance in the clinical records of 33 (46.5 per cent) of 71 necropsied cases, other observers either failed to notice such a high incidence or reported that left deviation of the electrical axis occurred almost as frequently.[18, 132, 126, 62, 86]

The roentgenogram in anterior views usually reveals a small, centrally placed cardiac silhouette.[127, 76, 112] This has been termed a cor pendulum or Tropfenherz ("drop" heart, not "dropped" heart). When cor pulmonale has developed, a careful fluoroscopic and roentgenographic study in the oblique and lateral as well as anterior views will usually reveal a prominence of the pulmonary artery and right ventricular contours.

Pneumoconiosis

Advanced pneumoconiosis is frequently complicated by cor pulmonale, as indicated by right ventricular hypertrophy and congestive heart failure.[34] According to Griggs, Coggin and Evans[57] this form of pulmonary fibrosis is associated with a higher percentage of cases of cor pulmonale than either emphysema or tuberculosis, although the absolute number of cases of cor pulmonale due to pneumoconiosis is less.

The development of right ventricular hypertrophy in pneumoconiosis is attributed to the increased pulmonary pressure due to narrowing and obliteration of the pulmonary capillaries by the fibrotic process.[71, 53]

The *clinical picture* of pneumoconiosis, with or without cor pulmonale, is dominated by exertional dyspnea and mild cyanosis. Cough and hemoptysis are frequent in cases complicated by tuberculosis. According to Giering and Charr[54] there is often a secondary polycythemia, but Coggin and his associates[34] rarely found the number of erythrocytes or their hemoglobin content increased. Clinical evidence of cor pulmonale is usually inconclusive in the absence of heart failure. The second pulmonic sound is often accentuated. Electrocardiographic and roentgenologic examinations may suggest enlargement of the right cardiac chambers.[143, 107, 39] Cardiac failure is a late development and death occurs soon after its appearance.

Other Bronchopulmonary Diseases

Chronic bronchiectasis and other bronchopulmonary diseases besides those mentioned above have occasionally been reported as causes of cor pulmonale with congestive heart failure, but only when they produce extensive pulmonary fibrosis. *Sarcoidosis* sometimes produces a rigid extensively fibrosed lung with sclerosed and obstructed vessels which is complicated eventually by enlargement and failure of the right heart.[124] Not infrequently the myocardium is likewise involved by the granulomatous and scarring process (p. 844) and it is difficult to determine whether heart failure is due to the myocardial lesions or to cor pulmonale. I have also observed right ventricular hypertrophy and

right-sided congestive heart failure following chronic pulmonary suppuration with perforation into the pleural cavity and chronic empyema. Willius[146] reported a case of cor pulmonale including congestive heart failure, secondary to diffuse bilateral congenital cystic malformation of the lungs.

Foreign bodies in the trachea may set up a valve-like mechanism which produces a bilateral obstructive emphysema, but there is no evidence that cor pulmonale results.[101] Stenosis of the trachea by a large goiter or a substernal thyroid causes respiratory difficulty but does not induce cor pulmonale. On the other hand, direct compression and stenosis of the pulmonary artery by an aortic aneurysm or similar tumor may cause right ventricular hypertrophy, as in two cases reported by Scott and Garvin.[130]

Pneumothorax and various forms of pleuropulmonary disease which cause cardiac displacement may occasionally produce circulatory symptoms and electrocardiographic and roentgenologic abnormalities of the heart, but rarely if ever cor pulmonale.[96]

Left-sided extensive pulmonary fibrosis, with or without bronchiectasis, atelectasis and pleural adhesions which draw the heart to the left, may cause serious circulatory disturbances. There may be such marked cardiac rotation along the vertical and transverse axes of the heart that the apex comes to lie in the fourth or third interspace and in the axillary region. In addition to dyspnea, tachycardia and cardiac irregularity (in one case I observed auricular flutter with irregular ventricular response), there may be a rise in venous pressure. Hurst and Brand[67] attribute the latter to direct compression or torsion of the subclavian or innominate veins. The electrocardiogram may reveal right axis deviation and inversion of T_1 or T_3. But these changes disappear partially or completely if a compensatory pneumothorax is produced artificially on the side opposite the lesion.

Kyphoscoliosis

Occurrence of Cor Pulmonale. Hypertrophy and dilatation of the right ventricle have been found in about 75 per cent of cases of severe kyphoscoliosis.[115, 29, 75] Rieder[115] noted hypertrophy and dilatation of the right ventricle in 29 out of 35 cases of kyphoscoliosis and Chapman and his associates[29] in 47 out of 69. In Bachman's[6] exhaustive study of kyphoscoliosis, he observed that of 154 carefully examined hearts, 56 per cent revealed dilatation and hypertrophy of the right ventricle, 26 per cent of both ventricles and 17 per cent of the left ventricle. The left ventricular hypertrophy was probably due to a high percentage of associated cardiac and vascular lesions. But even in the absence of such independent cardiac disease, right ventricular hypertrophy is observed secondary to the kyphoscoliosis.

The significant type of scoliosis is usually situated in the lower cervical and upper thoracic regions or in the midthoracic region, with the curvature convex to the right.[41] Males are predominantly affected. The deformity appears in childhood and reaches its maximum before growth is completed.[63] In most cases the cause is unknown and may be hereditary and congenital, but tuberculosis of the spine, rickets and poliomyelitis[64a] have also been listed as causative factors.

Pathogenesis of Cor Pulmonale. The development of the chest is stunted, the chest cavity is shortened, the diaphragms are elevated and the volume of the chest cavity and consequently of the lung is diminished. The lung on the side

of the deformity is greatly compressed, suffers atelectasis and eventually becomes fibrotic. The following factors have been implicated as causes of increased pulmonary vascular resistance with consequent strain on the right ventricle: (1) Diminution in the pulmonary vascular bed due to atelectasis and fibrosis of the affected lung and compensatory emphysema of the unaffected lung tissue. (2) Kinking and stenosis of the pulmonary artery. (3) Loss of respiratory aid to circulation because of impaired mobility of the diaphragm and chest wall.

Clinical Picture. Little has been added to the cardiopulmonary symptoms of kyphoscoliosis since Bouvier[19] in 1858 noted that patients with this deformity are subject to dyspnea, episodes of asthma, cough, palpitations, arrhythmia and syncopal attacks, and usually die of cardiac failure. Dyspnea results from a deficiency in pulmonary ventilation. The capacity of the lung may be diminished 20 to 60 per cent;[48] the vital capacity is similarly diminished and the residual air greatly increased.[20] Arterial anoxemia may be severe and may give rise not only to cyanosis and secondary polycythemia but also to attacks of dizziness, faintness or syncope.[17]

Roentgenologic examination reveals abnormalities which are due mostly or entirely to the change in the position of the heart.[119, 41] In the more frequent right kyphoscoliosis, the anterior view shows the cardiac silhouette displaced to the left, simulating enlargement.[2] The pulmonary salient appears convex as in mitral stenosis and resembles also the normal silhouette as seen in the right oblique position. Rotation of the patient to the right so as to bring the spine in the midline usually causes the cardiac silhouette to assume the normal appearance.

Similarly in cases of left kyphoscoliosis, the silhouette has a median position as if the normal body has been rotated toward the left oblique position. Rotation of the body to the left so as to bring the kyphoscoliotic spine into the midline usually restores the normal cardiac shadow. The upper mediastinal shadow often appears enlarged and has been misinterpreted as an aneurysm due to the fact that the aortic shadow is displaced from the spine and adds to the width of the spinal shadow.

When cor pulmonale has developed, rotation of the body as mentioned above will restore not the normal cardiac silhouette but one which reveals enlargement of the pulmonary arc and right ventricle as in other forms of pulmonary heart disease.

The *electrocardiogram* usually reveals no abnormality but there may be right deviation of the electrical axis.

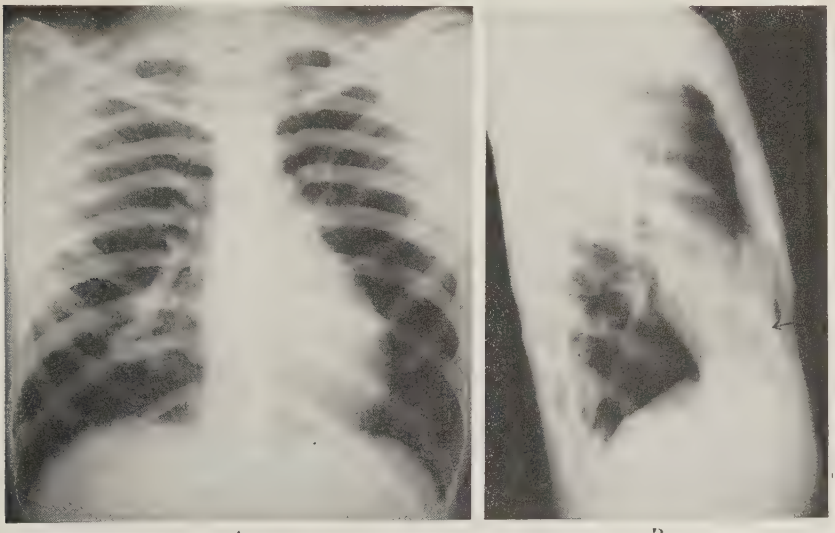
Most patients with severe kyphoscoliosis die eventually because of bronchopulmonary infection, to which they are unusually susceptible, or because of heart failure.[120, 6, 75, 63] The prognosis is poor once cardiac strain has developed. The average age of death is between thirty and forty although the outlook is somewhat better in women with kyphoscoliosis.[29, 6]

Treatment. The treatment of heart failure due to kyphoscoliosis is usually unsatisfactory and is similar to that described for emphysema heart. The danger of using morphine has been stressed by Schroeder[129] and by Daley.[36]

Funnel Chest

In cases of funnel chest (pectus excavatum—trichterbrust) there is a deep depression in the lower third of the sternum, at which level the anteroposterior

diameter is diminished. Funnel chest is probably a developmental abnormality but may occasionally be due to occupation or trauma. Although cardiac abnormalities have been attributed to it,[25] funnel chest is not responsible either for organic heart disease or, as a rule, for significant circulatory dysfunction. When the external anteroposterior diameter of the chest is less than 6½ inches, compression and displacement of the heart are apt to occur.[46] Physical examination frequently reveals a functional systolic murmur, usually over the pulmonic area, and displacement of the apical impulse to the left. The importance of funnel chest lies in the frequent misinterpretation of these signs as indicative of heart disease.[96a] Roentgenologic examination is diagnostic[42, 119, 140] (Fig. 75). In the anterior view the cardiac silhouette appears displaced to the left and



A B

Fig. 75. Funnel chest (pectus excavatum). *A*, Posteroanterior view. Apparent enlargement due to anteroposterior compression of heart. Cardiac volume normal. Most of cardiac silhouette in left chest. Spine shadow prominent. Ribs more horizontal than normal. *B*, Lateral view showing sternal depression.

the shadow is less dense than normally because of the diminution in anteroposterior mass. The heart may seem enlarged, but the heart volume is normal and lateral views reveal the anteroposterior narrowing, and sternal depression. The deformity may be corrected surgically.[105]

Pectus carinatum (pigeon chest) causes no cardiac abnormalities.

Cor pulmonale has been reported as a sequel of thoracoplasty.[23]

DISEASES OF THE PULMONARY ARTERIES

In the pulmonary diseases thus far considered, the development of cor pulmonale is attributed chiefly to increased pulmonary hypertension resulting from a diminution in the capillary bed of the lungs. These cases form by far the largest group in the category of chronic pulmonary heart disease. However, lesions of the pulmonary arteries themselves, particularly in the small branches, have been reported as the cause of right ventricular hypertrophy and cardiac failure. The following discussion is not concerned with all the varieties of pul-

monary arterial disease, but only with those which have been considered responsible for the development of chronic cor pulmonale.

Secondary Arterial or Arteriolar Sclerosis

The criteria, incidence and pathogenesis of pulmonary arteriosclerosis have been subject to considerable discussion and disagreement.[113, 87, 135, 122, 21] Microscopic evidence of pulmonary arteriosclerosis is observed almost universally,[21] but severe macroscopic sclerosis is noted in only 6 to 8 per cent of routine autopsies and is generally associated with or secondary to diffuse pulmonary disease.[99, 102, 103, 122] The sclerosis of the main pulmonary artery and its primary branches, even in the so-called severe cases, is not a factor in causing chronic cor pulmonale because these vessels are often actually dilated and there is no interference with the pulmonary blood flow.

The small pulmonary arteries and arterioles may also be the site of arteriosclerosis in cases of chronic pulmonary disease such as emphysema.[108] In these cases the arteriolar lumen may be narrowed but there is no significant correlation between the presence and degree of arteriolar narrowing and the occurrence or severity of right ventricular hypertrophy and failure. The pulmonary arteriolosclerotic lesions are probably secondary to pulmonary hypertension and not the cause.[108, 102] As a rule, the right ventricular enlargement in emphysema is due to the changes in the capillary system and the secondary arteriolar narrowing is unlikely to cause significant obstruction.

Primary Pulmonary Arteriolar Sclerosis

Primary pulmonary arteriolar sclerosis sufficient to cause chronic cor pulmonale is a rare condition[40, 10] and its existence has been questioned.[102] The criteria for this condition are: (1) severe and extensive arteriolar sclerosis with narrowing of the lumen; (2) hypertrophy of the right ventricle; (3) absence of cardiac disease which might account for right ventricular hypertrophy; (4) absence of bronchopulmonary disease which might cause pulmonary hypertension and secondary arteriolar sclerosis; (5) absence of specific infections or other specific conditions which might secondarily cause vascular changes resembling those of arteriolar sclerosis. An analogy has been postulated between essential hypertension of the pulmonary circulation with associated "primary" pulmonary arteriolosclerosis and the essential hypertension and arteriolosclerosis of the systemic circulation.[55] In the early stage of pulmonary hypertension there may be no significant histologic abnormalities.[40, 37, 3] In some cases right ventricular hypertrophy appears to be of unknown origin (idiopathic) and the existence of pulmonary hypertension is assumed without other supporting evidence.[37, 121]

Of 68 reported cases of primary arteriolar sclerosis, Brenner[21] accepted 16, including one of his own, as definite instances of right ventricular hypertrophy secondary to primary arteriolar sclerosis (see also Eppinger and Wagner,[43] Bredt[20]). The lesions known as endarteritis obliterans, consisting of great intimal thickening with narrowing or obliteration of the lumen, are of inflammatory origin and should not properly be included in the category of primary arteriolar sclerosis. Lesions which are indistinguishable from endarteritis obliterans on the one hand and primary arteriolar sclerosis on the other may occur rarely with rheumatic mitral stenosis, chronic pulmonary infections espe-

cially in the neighborhood of abscesses and caseous tuberculosis, and with the organization of pulmonary emboli or thrombi. Even among Brenner's[21] 16 accepted cases of so-called primary arteriolar sclerosis, there are some in which the reported data suggest strongly that the vascular lesions were secondary either to chronic bronchopulmonary disease or to chronic thrombi or emboli of the pulmonary arteries. The clinical picture associated with these so-called primary arteriolar lesions is similar to that in other forms of chronic cor pulmonale.

Pulmonary Arterial Obliteration—Pulmonary Thrombi and Emboli

The occurrence of acute right ventricular strain following massive pulmonary emboli has been discussed (Chapter 38). As first indicated by Ljungdahl,[88] there is probably also a chronic form of pulmonary heart disease resulting from chronic pulmonary emboli which obstruct a sufficiently large part (between 50 and 75 per cent) of the pulmonary arterial circulation. The cases of right ventricular hypertrophy with intense cyanosis, polycythemia and congestive heart failure, sometimes termed Ayerza's syndrome and reported by Jump and Baumann,[73] Barnes and Yater,[9] Means and Mallory,[98] and by Montgomery,[100] were attributed to large organized thrombi in the stem or main primary divisions of the pulmonary artery. The frequent site of the thrombus at the bifurcation of the pulmonary artery, certain clinical features in the reported histories and the recent studies by Belt[12, 13] indicating the comparative rarity of autochthonous thrombi and the frequency of emboli in the main pulmonary arteries suggest strongly that these were all instances of massive pulmonary embolism which were insufficient to cause death, but which produced chronic cor pulmonale.

The occurrence of chronic embolization of the pulmonary arteries was reported by Belt,[14] who described 4 cases of this condition. Emboli occurred at intervals over a period varying from three months to six years. A recent case was documented by Castleman and Bland.[27] Cases of chronic embolization are of great importance as a possible explanation of various thromboendarteritic and other occlusive lesions of the small pulmonary arteries and arterioles which have been reported as causing chronic cor pulmonale and so-called Ayerza's syndrome.

A careful study of the clinical history and pathologic findings in the cases described by Frothingham[52] as progressive thrombosis of the small branches of the pulmonary artery, by Rothschild and Goldbloom[123] as obliterative pulmonary arteritis, and perhaps also the case of obliterative arteriolar sclerosis of the lungs by MacCallum[91] and that of multiple pulmonary thrombi by Balboni,[7] suggests that they may all be examples of chronic pulmonary embolization with secondary changes of healing and vascular reaction. In all of these there was a similar picture of cyanosis, dyspnea, occasionally polycythemia, clubbing and attacks of syncope or chest pain terminating with right-sided heart failure.

Pulmonary Obstruction Due to Carcinomatous Lymphangitis or Embolism

Cases of occlusion of numerous small pulmonary arteries by tumor emboli or as a result of carcinomatous obstruction of the perivascular lymphatics with subsequent vascular thrombosis have been described as resulting in cor pul-

monale and right-sided congestive heart failure.[128, 83, 22, 56, 147, 95] As a rule, the primary neoplasm was a scirrhous carcinoma of the stomach which was undiagnosed and which had caused no clinical symptoms or only vague digestive disturbances.

Pulmonary involvement was characterized by dyspnea, tachypnea in brief acute attacks, cough and sometimes cyanosis. In some of the cases there was roentgenologic evidence of carcinomatous lymphangitis of the lungs, but few physical signs in the chest. Occasionally the electrocardiogram revealed right axis deviation with or without inversion of T_2 and T_3. Death occurred within a few weeks or months, usually after the development of right-sided congestive heart failure.

The essential findings at postmortem examination, aside from the primary carcinoma, are right ventricular dilatation and hypertrophy and the pulmonary vascular and lymphatic lesions.[128, 95] The diagnosis should be considered when patients without apparent pulmonary or cardiac disease, following a period of digestive disturbance, suffer from acute dyspnea, tachypnea, cough and cyanosis with progressive right-sided heart failure. When present on roentgenologic examination, the characteristic perivascular streaks, radiating from the hila throughout the lung fields, are indicative of carcinomatous lymphangitis with which this clinical picture is associated. Electrocardiographic evidence of right ventricular hypertrophy is confirmatory.

Pulmonary Obstruction with Schistosomiasis

Obstruction of the pulmonary arterioles by massive and probably recurrent infection with the ova of Schistosoma haematobium or mansoni is capable of producing right ventricular strain and congestive heart failure.[11] Shaw and Ghareeb[131] found pulmonary involvement in one third of 282 autopsied cases of schistosomiasis. In 6 of these the pulmonary obstruction was sufficient to cause a clinical picture resembling so-called Ayerza's syndrome, with extreme right ventricular hypertrophy and death from congestive heart failure.

According to Clark and Graef,[33] who described a similar case in a Puerto Rican youth, cases of bilharzial infection in North America arrive from Africa or the West Indies and are due to the S. mansoni, which usually localizes in the colon and rectum and causes a nodular cirrhosis of the liver as well as pulmonary disease. The schistosome ova reach the lungs as emboli from the portal or systemic veins, those of the mansoni variety probably through collaterals with the systemic circulation after portal obstruction occurs. The ova are impacted when they reach the arterioles or slightly larger arteries and set up perivascular tubercles, focal granulomatous necrotizing arteritis, or an obliterative arteriolitis followed by recanalization (angiomatoids), or widespread pulmonary obstruction without thrombus formation.

In cases due to S. mansoni, the variety found on this continent, the diagnosis may be suggested by the development of symptoms and signs of congestive heart failure in conjunction with hepatic cirrhosis and splenomegaly, usually in young persons without heart disease. X-ray examination discloses an appearance resembling that of atrial septal defect including enlargement of the right atrium and ventricle and pronounced dilatation of the pulmonary artery.

Marked right ventricular hypertrophy has been observed in a gray wolf, resulting from massive obstruction of the pulmonary arteries by Dirofilaria.[61]

Pulmonary Obstruction in Sickle-Cell Anemia

The general circulatory disturbances in sickle-cell anemia are described elsewhere (p. 973). We are concerned here with the tendency of sickle-cell anemia to be associated with vascular thrombi in the pulmonary arteries as well as in other vessels.[135, 148] Yater and Hansmann[148] suggested, on the basis of two cases which they reported, that cardiac failure in sickle-cell anemia may be due not only to the anemia but also to thrombotic obstruction of the pulmonary arteries with consequent pulmonary hypertension and cor pulmonale.[40, 3, 10]

Specific Infections

Among the specific infections, *syphilis* has been often reported as a cause of pulmonary arterial disease,[110, 74, 78] but it is questionable how often if ever it results in cor pulmonale and congestive heart failure. Syphilitic pulmonary arteritis can be accepted only as a rare cause of cor pulmonale, and then only when it is associated with widespread narrowing of the small pulmonary arteries due to endarteritis obliterans. Occasionally also, I have seen cases in which pulmonary hypertension and right ventricular failure were precipitated by the rupture of a syphilitic aortic aneurysm into the pulmonary artery.

Tuberculous endarteritis obliterans has been observed in the small pulmonary arteries adjacent to tuberculous foci and may be secondary to rupture of a caseous peribronchial lymph node.[44] Thrombi may appear. So far as I am aware, the lesions are never extensive enough to produce cor pulmonale.

Rheumatic pulmonary arteritis, usually of the main stem and its primary branches and occasionally of the smaller arteries, has been described.[84, 58] The lesions may be of the necrotizing type, associated with so-called periarteritis nodosa.[51] Cor pulmonale, secondary to rheumatic pulmonary arteritis, has never been definitely proven.

Pulmonary lesions may be due to various infections, such as influenza, or to bacterial infections by direct implantation on the intima, or by embolization. The possibility of widespread pulmonary arteritis, due to bacterial or other infections with healing and secondary pulmonary occlusion, is to be considered as a cause of some of the unexplained cases of cor pulmonale.

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40

THE HEART IN HYPERTHYROIDISM

Hyperthyroidism is an important etiologic factor in the production of auricular fibrillation, cardiac enlargement and congestive heart failure, but there is still considerable uncertainty whether hyperthyroidism per se is responsible for these manifestations. In short, it is uncertain whether there is a specific etiologic type of heart disease caused by hyperthyroidism, or whether the latter is merely a contributory or precipitating factor in individuals already predisposed by coincident heart disease.

The term thyroid heart disease is restricted to cases in which hyperthyroidism is associated with recurrent paroxysmal or established auricular fibrillation, or with congestive heart failure. Since many symptoms, such as palpitation and tachycardia, dyspnea, and precordial distress, are commonly observed with uncomplicated hyperthyroidism, their presence is not in itself sufficient to warrant the diagnosis of heart disease. When thyroid heart disease is thus defined, its incidence appears to be diminishing. Formerly, many of the cases of nontoxic endemic goiter associated with some unrecognized concurrent cardiac disease were classified erroneously as hyperthyroid heart disease.

In the great majority of cases of thyroid heart disease, there has been found evidence of associated arteriosclerotic, hypertensive, rheumatic or syphilitic heart disease. Kepler and Barnes[40] found organic heart disease in 18 (67 per cent) of 27 fatal cases of hyperthyroidism in which there had been evidence of congestive heart failure. Maher and Sittler[52] reviewed a series of 180 cases of hyperthyroidism, in 75 per cent of which they found complicating organic heart disease. Furthermore, in all of the 38 cases in which congestive heart failure was present, and in 41 out of 42 cases in which auricular fibrillation was encountered, there was independent organic heart disease. Therefore, with one possible exception thyroid heart disease in this series was always associated with an underlying independent organic cardiac disease.

The great frequency, if not the invariable association of organic heart disease, the absence of consistent or convincing pathologic evidence of structural cardiac damage due to hyperthyroidism (p. 917), and the reversibility of the cardiac manifestations of hyperthyroidism have given rise to the belief that a characteristic form of heart disease, due exclusively to hyperthyroidism, does not exist. On the other hand Likoff and Levine[50] found 21 instances (6.3 per cent) of definite congestive heart failure among 331 hyperthyroid patients without organic heart disease. While this incidence is much less than the 50 per

cent incidence of heart failure which they observed in hyperthyroidism combined with organic heart disease, they concluded that thyrotoxicosis is not infrequently the sole cause of heart failure. In the absence of postmortem examinations, the exclusion of organic heart disease is necessarily uncertain; even the characteristic clinical case report of heart failure due to uncomplicated hyperthyroidism presented by these authors strongly suggests the presence of an associated rheumatic mitral stenosis.

Despite these uncertainties as to whether hyperthyroidism is ever more than a contributory factor in causing heart failure, or whether it produces a specific form of heart disease, it deserves a special discussion in a book on heart disease because of its profound effects on the circulation and because its recognition and correction in a patient with serious cardiac failure may be followed by dramatic therapeutic success.

ETIOLOGY AND PATHOGENESIS

Cause

Most of the symptoms of uncomplicated Graves' disease, including the circulatory disturbances, may be attributed to an excessive production and dissemination of thyroid hormone. However, the exact mechanism by which these cardiac disturbances are induced is uncertain. In addition there is evidence that the pituitary gland, the diencephalon and hypothalamus, and the adrenal and sympathetic nervous system may be concerned in the production of some of the manifestations of Graves' disease, and similarly these organs and tissues may also influence the heart and circulation.

Age and Sex

Uncomplicated hyperthyroidism is most common between the ages of twenty and forty.[57, 35] In contrast, thyroid heart disease is exceptional before the age of forty, and in the series of 108 cases reported by Barker et al.,[8] the average age was fifty-one and a half. These figures stress the importance either of a prolonged duration of the hyperthyroidism or of the appearance of coronary insufficiency in later years in the production of the so-called thyroid heart.

Females predominate in a ratio of 5 to 1 in uncomplicated Graves' disease; this predominance is reduced to 2 to 1 in cases of thyroid heart disease.

Mechanism

We are concerned here primarily with the mechanism by which auricular fibrillation, cardiac enlargement or heart failure, i. e., thyroid heart disease, develops in instances of previously uncomplicated Graves' disease. Two general possibilities should be considered:

1. Coexistent Heart Disease and Hyperthyroidism. Coexistent independent heart disease reduces the cardiac reserve, but compensation is maintained for the ordinary demands placed upon the heart. With the advent of hyperthyroidism, certain alterations occur which in one way or another (see below) increase the demands on the heart to a degree which the diseased heart can no longer meet. Cardiac enlargement, cardiac failure and auricular fibrillation then develop. These are all manifestations which might have appeared eventually in the absence of hyperthyroidism, but which develop earlier because of hyperthyroidism.

Conversely, in many instances, hyperthyroidism antedates independent heart

disease due to hypertension and coronary arteriosclerosis. The normal heart for many years is capable of adjusting itself to the requirements imposed by excessive thyroid secretion and increased metabolism. But with the added burden of hypertension and the diminished cardiac efficiency due to coronary ischemia and myocardial anoxia, the heart is no longer able to maintain its normal size and remain compensated. Cardiac enlargement, auricular fibrillation and congestive heart failure are ultimate consequences.

2. Hyperthyroidism as an Exclusive Cause of Heart Disease. The second possibility also exists that prolonged and severe hyperthyroidism may by itself produce auricular fibrillation, cardiac enlargement and failure in the absence of any independent cardiac disease. In such an eventuality the hyperthyroidism would be considered the primary cause rather than a precipitating or contributory factor in the production of thyroid heart disease. The uncertainty that such a primary heart disease exists, and its infrequency if it does, have been mentioned above.

Methods by Which Hyperthyroidism May Affect the Heart

1. Effects of Thyroid Hormone on Heart Muscle. The thyroid hormone may impair the heart muscle by direct effects. Since the heart participates in the general increase of tissue metabolism, its oxygen requirement is augmented. The depletion of glycogen in the heart muscle[2] in experimental hyperthyroidism has been attributed to relative anoxia.[60] There is experimental evidence that thyroid extract or thyroxin acts directly on heart muscle to cause tachycardia.[48, 54] However, these findings are inadequate to permit the statement that auricular fibrillation or heart failure in clinical hyperthyroidism is the result of a direct cardiac effect of the thyroid hormone.

2. Excessive Sympathico-adrenal Stimulation. Resemblances between the clinical manifestations of hyperthyroidism and those caused by stimulation of the sympathetic nerves or the administration of epinephrine suggest that the cardiac disturbances in Graves' disease may be due to exaggerated stimulation of the sympathico-adrenal system. There is, in fact, evidence that the thyroid hormone sensitizes the sympathetic system to the action of epinephrine. But careful analysis discloses that the resemblance between the symptoms of Graves' disease and sympathetic-adrenal stimulation is superficial and incomplete. For example, the cutaneous vasoconstriction with consequent pallor and coldness resulting from sympathetic stimulation contrasts notably with the cutaneous vasodilatation and warmth of hyperthyroidism. The tendency to diarrhea is a parasympathetic not a sympathetic effect. The exophthalmos attributed to excessive cervical sympathetic tone has a different pathogenesis.[61, 58] While sympathetic stimulation and epinephrine could account for tachycardia and are capable of producing ventricular fibrillation experimentally, they do not cause auricular fibrillation.

3. Disturbed Circulatory Dynamics. The most plausible explanation for the effects of hyperthyroidism on the heart is that altered circulatory dynamics impose an excessive cardiac strain. These altered dynamics (infra), which are in part compensatory adjustments to the elevated metabolism, increase the work of the heart and its need for oxygen, and diminish its efficiency. In the presence of associated organic heart disease or with the development of coronary arteriosclerosis in middle life, these hyperthyroid strains lead to auricular fibrillation and congestive heart failure.

PATHOLOGIC PHYSIOLOGY

Increased Metabolism and Oxygen Consumption. An elevated basal metabolism, exceeding normal by 30 to 75 per cent or more, is the basic physiologic change in hyperthyroidism. This denotes an increase in oxygen consumption. As we shall see, this abnormal tissue oxygen requirement is met by a corresponding increase in minute volume (cardiac output) and not by increased oxygen utilization, for the arteriovenous oxygen difference is diminished.[51, 22]

Increased Heat Production. This is a consequence of increased metabolism and is disclosed clinically by a warm flushed skin. A number of chemical, hormonal and nervous compensatory mechanisms are called into action to maintain a constant temperature despite the increased heat production. The latter, by warming the blood, excites nerve centers (hypothalamus and spinal cord) which stimulate the secretion of sweat; perhaps also heat receptors in the skin reflexly assist this mechanism. The warm sweat (vasodilatation of the skin capillaries) found in hyperthyroidism contrasts with the cold sweat found in psychoneurotic patients or those in shock, in whom there is cutaneous vasoconstriction. About 6 per cent of the cardiac output flows through the skin in patients with Graves' disease, instead of the normal 3 per cent.

Increased Cardiac Output (Minute Volume). An increased cardiac output is characteristic of Graves' disease.[18, 51, 26] Like many other physiologic adjustments, it represents on the one hand a compensatory process by which the circulation attempts to keep pace with the increased metabolic needs and increased heat production of hyperthyroidism, while on the other hand its useful effects are partially vitiated by the strain it imposes on the heart. In the normal individual an increased cardiac output, e. g., during exercise, is accomplished by both an increase in cardiac rate and an increase in stroke volume; the better trained the individual, the less is the tachycardia and the greater the relative importance of the increased stroke output. In patients with hyperthyroidism, tachycardia is a cardinal feature, the accelerated pulse rate corresponding closely in degree to the elevated metabolism. In most if not all cases of hyperthyroidism, the increased heart rate is itself capable of accounting for the observed increase in cardiac output. By means of the cardiotachometer, Boas[12] observed that the average sleeping pulse rate in normal subjects was 58 per minute, while that in patients with Graves' disease averaged 89, an increase of 53 per cent, which corresponds closely with observed average increases in both the basal metabolism and the cardiac output. The tachycardia may be due to direct action of the thyroid hormone on the heart muscle or it may be a consequence of the Bainbridge reflex initiated by the increased venous return.

Stroke Output. While these considerations suggest that the stroke output in Graves' disease need not be elevated to explain the augmented cardiac output, direct determinations have not yielded consistent results.[18, 69] Fullerton and Harrop[26] noted a drop in the systolic output as well as in the minute volume, in 8 patients with Graves' disease, after thyroidectomy. However, the average systolic output before operation in these patients was 57 cc., which was slightly less than Grollman's average of 62 cc. for normal subjects. From these figures it is apparent that the preoperative elevation in cardiac output was due to tachycardia and the reduction after operation was entirely or almost entirely caused by a reduction in the heart rate. Bansi[6] found that the stroke volume tended to be diminished in patients with Graves' disease. While Liljestrand and Sten-

ström[51] observed a striking elevation in the cardiac output per minute in 11 cases of uncomplicated Graves' disease, the average output per beat was only 63 cc. and the range from 49 to 83 cc., corresponding to Grollman's average of 62 cc. and range of 38 to 84 cc. for normal subjects. Even with allowance for certain inconsistencies, these observations strongly indicate that the stroke volume in Graves' disease is neither significantly nor frequently increased and that it is a relatively unimportant factor in the augmentation of the cardiac output. The stroke volume has been considered in some detail because it is an indirect measure of the diastolic tension and of the length of the cardiac fibers in diastole, which in turn are related to the development of cardiac dilatation and hypertrophy.

Increased Venous Return. Peripheral Vasodilatation and Increased Blood Flow. The increased minute volume is itself the consequence of an enlarged venous return. Heightened tissue metabolism yields an excess of local metabolites which in turn dilate small vessels, establish arteriovenous shunts and lead to an accelerated venous return of blood from the periphery to the heart. Roberts and Griffith,[73] with the aid of the capillary microscope, observed that most of the cutaneous capillaries in the forearms were dilated in hyperthyroidism. The peripheral blood flow, measured by several observers using different methods, was uniformly found to be increased in patients with hyperthyroidism.[78, 20, 1]

Diminished Circulation Time and Increased Blood Volume. The minute volume (cardiac output) varies with the velocity of blood flow and with the circulating blood volume. Actually, both of these factors have been found to be increased in patients with hyperthyroidism. A heightened velocity of blood flow, i.e., a *diminished circulation time,* was demonstrated by Blumgart, Gargill and Gilligan[11] with the aid of radium C and by Tarr, Oppenheimer and Sagar[79] with the aid of decholin. The circulation time from arm-to-tongue is usually between 7 and 10 seconds in contrast to the normal of 10 to 16 seconds. This acceleration of the circulation probably results from peripheral arteriovenous shunts caused by vasodilatation due to the accumulation of increased metabolites. An augmented circulating blood volume was determined by Rowntree and Brown[76] with the use of Congo red, by Chang[16] with the use of carbon monoxide, and by Gibson and Harris[27] with the aid of Evans blue. However, the increase in blood volume averages only about 10 per cent.[24] On the other hand, the speed of circulation increases 30 to 70 per cent and can account for almost all of the increase in venous return and cardiac output.[24]

Relations of Altered Circulation to Thyroid Heart Disease. To what extent are these circulatory adjustments in hyperthyroidism responsible for the manifestations of thyroid heart disease, namely, auricular fibrillation, cardiac enlargement and congestive heart failure? The tachycardia which is uniformly present in uncomplicated hyperthyroidism is rarely of sufficient degree to induce heart failure.[81] A consideration of the stroke output likewise yields no clue as to a mechanism by which hyperthyroidism might produce the manfestations known as thyroid heart disease. As we have seen, there is little evidence indicating that the stroke output is either consistently or significantly elevated. The augmented cardiac output per minute and, therefore, the increased cardiac work per minute is in itself incapable of producing cardiac hypertrophy or cardiac failure as long as the work of the heart *per beat* is not greater.[81]

There is, however, evidence suggesting that the heart in hyperthyroidism is

inefficient in its adaptation to an increased strain. The hyperthyroid heart at rest is already utilizing its reserves in a manner which resembles that of the normal heart performing heavy work. Plummer and Boothby[66] and Briard and his associates[14] demonstrated that patients with hyperthyroidism were inefficient in converting potential energy into motion. Bansi and Groscurth[7] found that the cardiac output, the oxygen consumption and the blood pressure during and after work were all increased in hyperthyroid patients to a relatively much greater extent than in normal individuals performing the same work. Boothby and Rynearson[13] observed a greater augmentation in the cardiac output in patients with Graves' disease than in normal subjects following similar increases in oxygen consumption caused by work.

These varied observations, as well as a consideration of the circulatory changes already mentioned, suggest not only that the hyperthyroid heart is under strain to provide an adequate blood supply for the exaggerated oxygen demands of the tissues, but also that the adjustments employed are wasteful in their provision and utilization of this increased oxygen supply. The heart muscle itself becomes especially sensitive to any deficiency in oxygen supply, partly because of its own increased metabolism and partly because it is constantly performing an excessive amount of work. While it is possible for the normal heart with rare exceptions to meet the added strains of hyperthyroidism, this adjustment becomes more and more difficult if the heart is already impaired and enlarged by preexisting disease, or if cardiac function becomes diseased as the result of progressive coronary deficiency in later years. Cardiac hypertrophy due to rheumatic heart disease or hypertension or other cause increases the myocardial need for oxygen, while coronary artery disease diminishes the supply; in either circumstance the hyperthyroid heart, already suffering from low oxygen reserve, is especially vulnerable. In summary it appears that the circulatory adjustments to the increased metabolism of Graves' disease impose a heavy burden on the heart, but a burden which is likely to produce congestive heart failure only when the heart is already vulnerable or becomes vulnerable because of associated independent disease.

Mechanism of Auricular Fibrillation in Hyperthyroidism. The mechanism by which hyperthyroidism or its altered circulatory dynamics may cause or predispose to auricular fibrillation is unknown. The high incidence of auricular fibrillation, especially of the paroxysmal type, is a distinctive feature in hyperthyroidism. The frequency and transiency with which it appears shortly after thyroidectomy and the frequency with which preoperative transient or permanent auricular fibrillation is cured by thyroidectomy attest to more than an accidental relationship between hyperthyroidism and auricular fibrillation. These observations may denote that the thyroid hormone represents a direct toxic cause of auricular fibrillation in susceptible individuals.

It is also possible that the auricular fibrillation results from the augmented venous return to the heart with its prolonged exaggerated stimulation of the auricular muscle about the entrance of the great veins, where a circus movement of muscular contraction waves may be induced. Excessive vagal tonus has been credited with an important role in causing auricular fibrillation, on the basis of experimental production of this arrhythmia by vagal stimulation in cats and its production in hyperthyroid patients by the administration of mecholyl.[62] However, as a rule, auricular fibrillation is found only in hyperthyroid patients in the older age groups and with associated cardiac disease.

This strongly suggests that the latter is the basic cause of the auricular fibrillation and that the hyperthyroidism merely increases its occurrence or hastens its development. When the associated cardiac disease is sufficient in itself to cause auricular fibrillation, thyroidectomy does not cure this arrhythmia.

PATHOLOGY OF THE HEART IN GRAVES' DISEASE

There are no constant or characteristic morphologic changes in the heart which might be attributed to hyperthyroidism. Infiltrations of lymphocytes and histiocytes, as well as areas of myocardial necrosis and extensive interstitial fibrosis, have been reported,[23, 28, 47] but careful controlled histologic studies have failed to substantiate these findings.[70, 80] Likewise, I have been unable to find pathologic evidence of characteristic cardiac changes due to hyperthyroidism, in a postmortem study of more than 35 hearts in patients with this disease. Necrosis, fibrosis and reactive cellular infiltration observed in some hearts could be explained by the ischemic effects of associated coronary arteriosclerosis.

It is well to remember that the absence of distinctive morphologic changes in the hearts of hyperthyroid individuals does not exclude the possibility that hyperthyroidism produces important or distinctive metabolic changes which alter the function of the heart muscle fibers. The evidence of glycogen depletion in the heart muscle, in experimental hyperthyroidism, has been noted.

Size of the Heart. Postmortem studies almost uniformly disclose a high incidence of cardiac hypertrophy in Graves' disease. Willius and his associates[83] observed cardiac hypertrophy in 16 of 21 cases, Kepler and Barnes[40] in 42 of 86 cases and Parkinson and Cookson[64] in 22 of 43, making a combined average of about 50 per cent of hypertrophied hearts.

In a study of 27 autopsied cases,[25] we found that 14 of the 27 hearts were hypertrophied, as determined by comparison with figures for normal heart weight relative to body weight. However, we observed that 12 of the 14 hypertrophied hearts were those of persons in whom the hyperthyroidism was complicated by hypertension, severe coronary narrowing and/or auricular fibrillation. Six of these 12 hypertrophied hearts were those of patients who had suffered from congestive heart failure. The most extreme hypertrophy in the series was found in those hearts in which congestive failure had been present. We concluded that cardiac hypertrophy is usually absent or of minimal degree in uncomplicated cases of Graves' disease. However, eventually cardiac enlargement and hypertrophy developed in about half the cases which come to autopsy in a general hospital, because of complicating heart disease or hypertension. Cardiac hypertrophy is found in those cases of hyperthyroidism in which there is also thyroid heart disease, i.e., in which established auricular fibrillation or cardiac failure coexists.

The absence of cardiac hypertrophy in uncomplicated hyperthyroidism may be related to the finding that the stroke output and therefore the diastolic tension are usually normal. When cardiac hypertrophy occurs, it is the consequence of hypertension or associated valvular disease; most strikingly, it appears with progressive myocardial failure.

CLINICAL FEATURES OF THE HEART IN HYPERTHYROIDISM

Many of the symptoms and signs referable to the heart and circulation are essential features of uncomplicated Graves' disease; their presence does not

warrant a diagnosis of thyroid heart disease. Arbitrarily one may speak of thyroid heart disease when in addition to hyperthyroidism there is also persistent auricular fibrillation, distinct cardiac enlargement or congestive heart failure.

Symptoms

Palpitation is one of the commonest subjective symptoms referable to the heart in Graves' disease. As a rule it occurs independently of heart disease and is the consequence of rapid and forceful heart action as well as of hypersensitivity of the autonomic and central nervous system. Palpitation may vary in severity from an uncomfortable awareness of the heart beat to an intense and sometimes terrifying pounding. It may be present when the patient is at rest, especially when lying on his left side, but more often it appears or becomes accentuated with emotion and exertion or after a meal.

Another type of palpitation occurs in paroxysms and is due to transient episodes of auricular fibrillation or, rarely, of flutter.[41] It may be associated with faintness, weakness or precordial distress. When these attacks of auricular fibrillation are accompanied by very rapid ventricular rates, the local distress is sometimes overshadowed by breathlessness. Extreme weakness may follow subsidence of such an episode. Occasionally a severe attack of paroxysmal auricular fibrillation may precipitate transient pulmonary edema or chronic congestive heart failure. As a rule, however, these transient paroxysms of irregular heart action come and go and the patient learns to tolerate them.

Similarly, *permanent* auricular fibrillation may provoke the subjective sensation of palpitation with or without an awareness of an irregular heartbeat, or it may be accompanied by more serious symptoms of congestive heart failure. On the other hand, many patients with auricular fibrillation, transient or permanent, are unaware of the irregularity.

Breathlessness is also a common symptom, but its character and pathogenesis are distinctive from those of classic cardiac dyspnea. It is often experienced on exertion and is associated with easy fatigability. The combination reminds one of similar symptoms observed in neurocirculatory asthenia or cardiac neuroses. In some of these cases the breathlessness occurs predominantly at rest and is the sighing type seen in psychoneurotic individuals.

On the other hand, the dyspnea may be due to an actual disturbance in circulation. The oxygen consumption and cardiac output in hyperthyroid patients during and after work are increased much more than in normal persons performing the same exertion.[7] Furthermore, the vital capacity has been found to be below normal in hyperthyroidism.[68, 11] Because of these findings, the dyspnea has been explained as being due to increased pulmonary ventilation necessitated by coincident augmented oxygen consumption and decreased vital capacity.[56]

But the dyspnea of uncomplicated hyperthyroidism, unlike that of heart failure, is not associated with evidence of pulmonary congestion; in fact, the rate of blood flow through the lungs is accelerated and not delayed. Therefore it appears improbable that the dyspnea is due to any circulatory abnormality. It seems more likely that the respiratory distress in uncomplicated hyperthyroidism is induced by the easier fatigability of the muscles of respiration rather than by any intrinsic pulmonary disturbance. The fatigability of the respiratory muscles may be the result of the increased work needed for the augmented

oxygen supply or of an actual respiratory muscular weakness which is part of a general disturbance in creatine metabolism often present in hyperthyroidism.[77] Dyspnea occurs more readily when the patient lives in an atmosphere of low oxygen pressure which interferes with his high oxygen requirement. In fact dyspnea on exertion (occurring in 56 per cent of 146 cases) was described as the commonest symptom of hyperthyroidism in patients residing at the high altitude of Denver where the atmospheric pressure is low.[15]

Finally true cardiac dyspnea may become a prominent symptom as a result of the development of pulmonary congestion due to heart failure. In such cases all of the features of cardiac dyspnea are present and there are often râles at the bases of the lungs, while the circulation time, although not prolonged, is delayed in comparison with the rapid circulation time of uncomplicated hyperthyroidism.

Precordial pain is an occasional symptom of hyperthyroidism. It may represent only a mild discomfort associated with tachycardia and awareness of the heartbeat. There may be a sticking type of pain in the region of the cardiac apex, such as occurs in many women with hypersensitive nervous systems. On the other hand, more intense precordial pain may accompany a paroxysm of auricular fibrillation with very rapid ventricular rate. Occasionally such an episode may simulate an attack of acute myocardial infarction.

In a small percentage of cases, angina pectoris characterized by a compressing retrosternal and precordial pain with typical radiations and induced by effort and excitement may be associated with hyperthyroidism. Since this is seen most commonly in the older age groups, it is probable that the angina pectoris results from concomitant severe coronary artery disease. However, Lev and Hamburger[45] reported that the angina pectoris disappeared following subtotal thyroidectomy. This suggests that the hyperthyroidism was at least a contributory factor in causing the pain, perhaps by increasing the oxygen requirements of a myocardium already deficient in blood supply.

Objective Manifestations

We are concerned here primarily with cardiac and other circulatory manifestations of hyperthyroidism, but the predominant signs of this disease are usually outside the heart. The latter include the characteristic stare, the warm moist and often ruddy skin, the enlarged thyroid gland and the tremor. In cases of thyroid heart disease, many of these classic signs of hyperthyroidism are often obscure, or may be overshadowed by the cardiac manifestations. In particular, exophthalmos is usually absent and the thyroid gland is not noticeably enlarged.[33] Cases of cardiac disease or congestive heart failure with hyperthyroidism in which the classic signs of the latter seem to be absent or are easily overlooked are sometimes described under the heading of "masked hyperthyroidism."[46, 5]

The Heart. Examination often discloses a broad, striking precordial pulsation which is easily visible as well as palpable. The apical thrust is often sharp and snapping. These pulsations correspond to a steep rapid ascent of the ventricular contraction curve. The strong pulsations may suggest the presence of cardiac hypertrophy, but usually neither the position of the apical impulse nor percussion of cardiac dullness reveals any evidence of cardiac enlargement in uncomplicated cases.

The *heart sounds* are loud and are distinguished especially by the first sound

at the apex, which is sharp and snapping, often simulating the sharp first sound of mitral stenosis. A systolic murmur is common and is usually most audible over the pulmonic area. It has been classified as a functional murmur, and attributed to dilatation of the pulmonary artery.[83] From time to time the sharp first apical sound in hyperthyroidism is associated with a distinct presystolic murmur, under which circumstance the similarity to mitral stenosis presents a problem in differential diagnosis. In my experience the association of rheumatic mitral stenosis with hyperthyroidism has been more common than is generally stated.

Heart and Pulse Rate. As a rule, the pulse rate in Graves' disease is between 90 and 120 per minute, but wider variations are encountered. While the pulse rate in hyperthyroidism is abnormally increased by activity and emotional excitement, it also remains elevated when the patient is apparently calm and at rest. Boas[12] has observed with the aid of the cardiotachometer that relatively little slowing of the heart rate occurs during sleep in contrast with the striking slowing of the tachycardia in psychoneurotic individuals.

Pulse rates of 180 to 200 or more are sometimes observed in hyperthyroid patients either because of an extremely elevated metabolic rate, because of a paroxysm of auricular fibrillation, or most commonly during a thyroid crisis or thyroid "storm" following thyroidectomy. The latter is a clinical syndrome which may result from sudden excessive flooding of the tissues with thyroid hormone during thyroidectomy, possibly associated with postoperative infection and dehydration; its exact pathogenesis and pathologic physiology are undetermined.

The pulse is not only rapid, but often presents the full steep ascent and sharp rapid drop characteristic of the Corrigan or water-hammer pulse found in aortic insufficiency. Correspondingly, there may also be striking visible pulsations of the vessels of the neck. These pulse characteristics result from the rapid discharge of blood from the heart into a dilated relaxed vascular bed.

Auricular Fibrillation and Other Arrhythmias. In more than 75 per cent of the cases there is regular sinus rhythm at all times, even when the heart rate is very rapid, but auricular fibrillation in paroxysmal or persistent form occurs with sufficient frequency to be considered a characteristic and diagnostic feature of hyperthyroidism. Ernstene[21] noted auricular fibrillation at some time in about 21 per cent of 1000 cases, but less than half of these were observed preoperatively. Permanent auricular fibrillation occurred twice as often in this group as the paroxysmal variety. Hurxthal[36] encountered *established auricular fibrillation* in 5.8 per cent of 7363 patients operated for hyperthyroidism; in terms of the thyrocardiac group this arrhythmia occurred in about 90 per cent of the cases. More than 10 per cent of the total group of hyperthyroid patients had experienced *transient* auricular fibrillation before or after operation.

While *permanent* auricular fibrillation may be associated with a variety of cardiac diseases, especially rheumatic mitral stenosis and advanced coronary arteriosclerosis, *paroxysmal* auricular fibrillation is highly suggestive of the presence of hyperthyroidism. Temporary auricular fibrillation may appear for the first time or recur immediately following thyroidectomy; in either circumstance it usually disappears spontaneously after a few days or weeks. Ernstene[21] observed that following thyroidectomy recurrent paroxysmal auricular fibrillation invariably reverted spontaneously to normal sinus rhythm if the patient

survived. On the other hand, thyroidectomy resulted in the spontaneous re-establishment of sinus rhythm in one third of the cases of established auricular fibrillation; of the remainder, a high percentage of restoration of sinus rhythm was effected by the administration of quinidine.

Auricular fibrillation is associated predominantly with hyperthyroidism in the older age group. Seventy-five per cent of the cases of auricular fibrillation in Ernstene's[21] series occurred in persons above the age of forty-five. The severity of the hyperthyroidism does not appear to be a determining factor, for auricular fibrillation is uncommon in young persons with Graves' disease, even when the basal metabolic rate is extremely elevated. When auricular fibrillation is encountered in patients under the age of thirty-five, it is almost invariably paroxysmal. Organic heart disease is frequent in cases of hyperthyroidism with auricular fibrillation, especially of the permanent variety. More than half of Ernstene's patients with auricular fibrillation presented evidence of associated arteriosclerotic, hypertensive or rheumatic heart disease. Apparently, underlying cardiac disease is an important predisposing factor in the development of auricular fibrillation, even though hyperthyroidism appears to be the trigger mechanism responsible for its appearance. Finally, there is evidence that auricular fibrillation increases in frequency with the duration of the hyperthyroidism.[83]

Other arrhythmias are extremely uncommon. Premature beats occur occasionally but are not characteristic of hyperthyroidism. Rarely, auricular flutter, paroxysmal auricular tachycardia or heart block is observed. Davis and Smith[19] described 6 cases of complete heart block in hyperthyroidism due to acute infections or digitalis. Unlike auricular fibrillation, these arrhythmias are not influenced by thyroidectomy.

Blood Pressure and Pulse Pressure. The systolic blood pressure may be normal, but more often it is at the upper limit of normal or moderately elevated. On the other hand, the diastolic pressure is almost always normal unless there is an associated essential hypertension. Occasionally the diastolic pressure is below normal. Consequently the pulse pressure is usually elevated.[65] In fact, an increased pulse pressure due to systolic hypertension is sometimes the clue to the discovery of hyperthyroidism. But of course these findings are by no means limited to hyperthyroidism. Occasionally an extremely wide pulse pressure, resembling that of aortic insufficiency, is associated with other dynamic changes characteristic of the latter disease, namely prominent carotid pulsations, Corrigan pulse, pistol shot in the femoral arteries and capillary pulse.

The Circulation Time and Venous Pressure. In uncomplicated hyperthyroidism, the velocity of blood flow is distinctly increased (p. 915). In my experience both the arm-to-lung time determined with the aid of ether (p. 139) and the lung-to-tongue time (p. 141) are significantly diminished, but the greater reduction in circulation time appears to involve the segment from the antecubital vein to the pulmonary capillaries. The arm-to-lung time in such cases is usually between 3 and 4 seconds when the arm-to-tongue time is between 8 and 10 seconds.

The circulation time may remain rapid or within normal limits even when there are distinct clinical features of congestive heart failure and the venous pressure is elevated. In such circumstances the circulation time may not be quite as abbreviated as in uncomplicated hyperthyroidism, but usually it averages 10 to 15 seconds, which is within the normal range of healthy persons.

This combination of congestive heart failure with a normal or rapid circulation time is distinctive of hyperthyroidism, although it may also be observed in heart failure associated with vitamin B deficiency, with fever, with severe cor pulmonale or with severe anemia.

The venous pressure is usually normal in cases of uncomplicated hyperthyroidism.

Roentgenologic Examination of the Heart. In uncomplicated hyperthyroidism, roentgenologic examination of the heart discloses either no significant

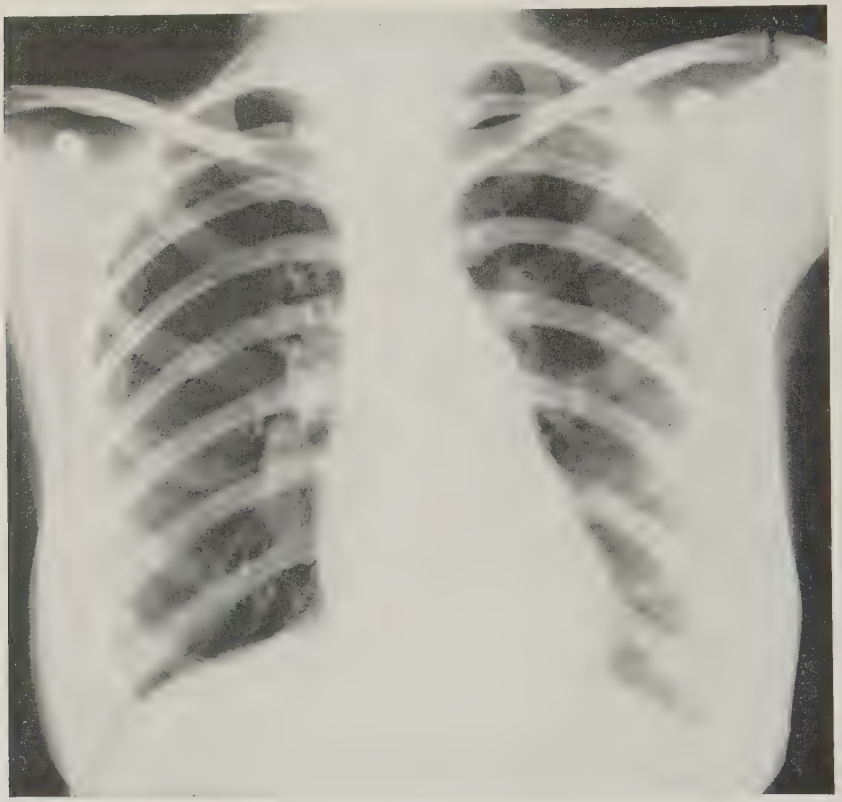


Fig. 76. Heart in hyperthyroidism. Pulmonary artery segment elongated and convex.

abnormality or a prominent pulmonary artery with increased pulsations (Fig. 76). The sharp pulsations may extend to the remaining contours of the heart shadow.[74] The prominence and accentuated pulsation of the pulmonary artery probably result from the augmented and accelerated blood flow which dilates that vessel. The active pulsation of the cardiac borders resembles that seen fluoroscopically in cases of aortic insufficiency, but in the latter it is the aorta which is prominent and pulsating vigorously. The prominence of the pulmonary artery may result in a straightening of the left border such as accompanies mitral stenosis. But examination in the oblique positions fails to reveal the enlargement of the left auricle seen in mitral stenosis; however, both auricles may become enlarged if congestive heart failure complicates hyperthyroidism.

In uncomplicated cases there is no distinctive enlargement of the cardiac chambers. Most observers, however, have described enlargement of the heart,

as determined roentgenologically, in 25 to 45 per cent of their cases.[64, 44, 53] The character of the cardiac enlargement observed is variable and in my opinion is determined by associated cardiovascular disease such as hypertension, severe coronary artery disease or rheumatic heart disease. When congestive heart failure is well established, the heart is usually enlarged to the right and the left and the cardiac silhouette assumes a globular appearance. However, corresponding to the rapid blood flow through the lungs and the rapid circulation time, the pulmonary fields are often remarkably clear, considering the clinical evidences of heart failure.

Electrocardiographic Examination. The electrocardiogram discloses no distinctive features except for the usual nonspecific sinus tachycardia or the occasional auricular fibrillation.[29] The former belief that the T waves become elevated in hyperthyroidism in contrast to the characteristically low T waves in myxedema has not been substantiated.[75] Parkinson and Cookson[64] noted an elevated P wave (more than 3 mm.) in over one third of their cases. In my experience, a distinctive elevation of the P wave usually occurred when there was associated mitral stenosis and in some cases of heart failure. Occasionally I have observed abnormalities of the QRS complex, the RST segment or the T wave, which, however, could reasonably be attributed to associated myocardial damage caused by coronary disease or to the effects of digitalis.

Development of Congestive Heart Failure. The most serious consequence of hyperthyroidism is the development of congestive heart failure. Congestive heart failure, like auricular fibrillation, develops most frequently in older age groups, and is rare under the age of forty;[2] it occurs more often with associated hypertension, coronary arteriosclerotic or rheumatic heart disease than in their absence;[40] it is more likely to develop the longer the duration of the hyperthyroidism, but is not distinctly related to its severity. Andrus[2] encountered congestive heart failure in 18.5 per cent of 200 cases of hyperthyroidism. In only 9 cases did symptoms of failure develop before the age of forty and in 7 of the 9 there was evidence of coexisting heart disease. Five of the 7 patients were found to have mitral stenosis when the basal metabolic rate was restored to normal; 1 had syphilitic heart disease; and in 1 case Aschoff bodies were found in the heart at postmortem examination. Ernstene[21] reported congestive heart failure in 25 per cent of those of his cases of hyperthyroidism which were combined with various forms of heart disease, but no instances of congestive failure in 795 cases of hyperthyroidism without evidence of associated organic heart disease.

Congestive heart failure usually develops after a period of established auricular fibrillation (p. 920). In a recent report, Hurxthal[36] noted that of 431 cases with established auricular fibrillation 55.7 per cent showed congestive heart failure. But for his entire series of over 7000 cases the incidence of congestive heart failure was only 3.7 per cent. The incidence of congestive heart failure in hyperthyroidism appears to be diminishing because of earlier recognition and treatment of hyperthyroidism.

THE DIAGNOSIS OF CARDIAC DISEASE IN HYPERTHYROIDISM

Diagnosis involves the recognition of both the hyperthyroidism and the cardiac complication. The diagnosis is simplest in cases in which there is a known history of hyperthyroidism or the characteristic stare and eye signs, the tachycardia, the warm moist skin, the tremor, the enlarged thyroid gland, intol-

erance to heat, excessive perspiration, loss of weight despite good appetite, nervousness, tendency to diarrhea, and an elevated basal metabolic rate unexplainable by the degree of heart failure present. In such cases of unmistakable Graves' disease, we may speak of thyroid heart disease if there is also frequent paroxysmal or persistent auricular fibrillation, unquestionable cardiac enlargement, as revealed by roentgenologic examination, or distinct evidences of congestive heart failure.

In many cases one may discover an independent form of heart disease which could account for the auricular fibrillation, cardiac enlargement or heart failure. But even in cases with independent heart disease it is important to discover the associated hyperthyroidism without which the organic heart disease might not have produced clinical symptoms. For in the presence of organic heart disease, the alleviation of the hyperthyroidism usually causes a reversal of most or all of the important cardiac disabilities.

A greater problem arises in those cases in which the predominant manifestations are cardiac and the presence and importance of the hyperthyroidism are discovered only secondarily. Such discovery will occur if the possibility of hyperthyroidism is considered in all cases in which auricular fibrillation, cardiac enlargement or heart failure of uncertain etiology is encountered. Often in thyrocardiac patients the thyroid gland is small and there is no exophthalmos, but there are usually a slight stare, warm moist skin, tachycardia, a high pulse pressure and a history of weight loss. A search for an associated hyperthyroidism should be considered under the following circumstances:

1. Paroxysmal or persistent auricular fibrillation of undetermined etiology.
2. Heart failure without apparent cause or heart failure which does not respond to digitalis and other appropriate treatment.
3. Heart disease with unexplained tachycardia.
4. Presence of congestive heart failure without significant fever, anemia or serious vitamin B_1 deficiency, in which the circulation time is within the normal range.

In any of the above groups, adequate evidence of hyperthyroidism may be forthcoming as soon as the possibility is considered. However, in the presence of heart failure, it may be difficult to evaluate an elevated basal metabolism. Sometimes the role of hyperthyroidism may not be demonstrable until the administration of iodine or propylthiouracil produces a striking amelioration of symptoms which had proved resistant to all other measures.

The differential diagnosis of hyperthyroidism is not pertinent to this volume. From the cardiac point of view it may be necessary to differentiate hyperthyroidism from mitral stenosis because of the presence in both of a sharp first sound, a systolic murmur and a prominent pulmonary artery. However, this is not an important problem because the diagnosis of hyperthyroidism should be made on other criteria. On the other hand, mitral stenosis may be diagnosed and hyperthyroidism overlooked when there is a characteristic apical diastolic murmur and thrill, especially in association with left auricular enlargement. The presence of mitral stenosis does not exclude an associated hyperthyroidism, nor conversely.

PROGNOSIS

Hyperthyroidism, if unrecognized or untreated, is likely to produce serious cardiac complications in patients already suffering from rheumatic heart dis-

ease or hypertension or in those who develop coronary artery disease as they grow older. This risk in itself is sufficiently great to warrant early recognition and treatment of hyperthyroidism. It is possible also that prolonged hyperthyroidism is capable of producing cardiac complications as patients grow older, even in the absence of independent cardiac disease.

In patients who already suffer from cardiac disturbances, such as auricular fibrillation, cardiac enlargement or congestive heart failure, the prognosis is even more dire if the hyperthyroidism is unrecognized or untreated. The cardiac disability increases progressively and relatively rapidly in spite of all measures directed to the heart and circulation itself. In fact these measures are unlikely to be efficacious without treatment of the hyperthyroid factor. On the other hand the treatment of hyperthyroidism is attended by such little risk in skillful hands, and the results are so eminently satisfactory or even brilliant in such a high percentage of cases, that the prognosis of thyrocardiac disease is converted from a hopeless to a very favorable one.

The results of operation have often been miraculous in patients who appear to be hopeless cardiac cripples. Patients with heart failure usually lost their symptoms rapidly and became restored to normal active life.[31] Similar results are to be anticipated when the hyperthyroidism is controlled by antithyroid drugs or radioactive iodine, the latter of which may become the preferred form of treatment. If, as is often the case, there is associated heart disease, the subsequent course of these patients is the course to be expected of the independent heart disease. Practically, this means restoration of function and a long interval before the basic cardiac disease again leads to failure.

TREATMENT

The treatment of thyroid heart disease is primarily *prophylaxis*. Early recognition of uncomplicated hyperthyroidism and its prompt control will prevent the development of cardiac complications due to the hyperthyroid element.

When auricular fibrillation or congestive heart failure is already present as well as hyperthyroidism, it must be clearly recognized that the elimination of the hyperthyroidism should be the primary objective of the therapeutic attack. Limitation of activity, the restriction of salt and fluids, digitalization and the use of diuretics and other therapeutic measures for heart failure are all appropriate. But all of these measures may be ineffective or of only limited value until the hyperthyroidism is corrected. Therefore, unnecessary procrastination in an effort to control either the auricular fibrillation or the heart failure before undertaking treatment of the hyperthyroidism may be not only wasteful but dangerous.

Surgical Treatment. Although surgical treatment of thyrocardiac disease has given brilliant results, it is probable that this form of treatment will be superseded by the use of radioactive iodine. Surgical control of the hyperthyroidism may be limited to those cases in which there is doubt as to the presence or absence of malignancy in the gland, and to those cases with compression symptoms. According to Williams[82a] subtotal thyroidectomy is the preferred treatment in the presence of a large nodular gland or when rapid recovery is a major objective.

Preoperatively the patient is treated with propylthiouracil, 300 mg. daily, until the desired reduction in basal metabolism and clinical improvement are obtained.[42, 70a] Compound solution of iodine in doses of 10 to 20 minims daily

is given for ten to fourteen days to reduce vascularization of the gland before operation. The compound solution of iodine may be administered concomitantly with propylthiouracil. A high caloric and vitamin intake is given. Heart failure, if present, is treated as described elsewhere (Chapter 9), but operation is not delayed even if heart failure persists. If haste is indicated, the patient may be prepared with Lugol's solution alone for about two weeks, as before the use of the uracil drugs.

At operation, a subtotal thyroidectomy is performed.[43] The importance of employing a skillful and experienced surgeon, and of avoiding a prolonged operative procedure, hemorrhage and other causes of shock cannot be exaggerated. It may be necessary to do the operation in two stages. Endotracheal anesthesia, using ethylene followed by ether, has given satisfactory results.[43]

Postoperatively, the patient should be placed in an oxygen tent. If fluids are given parenterally, they should consist of 5 per cent glucose in distilled water and should be administered very slowly to avoid pulmonary edema. The basal metabolism rate should return to normal in two to four weeks. If the patient was digitalized preoperatively, maintenance doses of digitalis are continued after operation until it is apparent that the hyperthyroidism has been eliminated. By that time evidence of heart failure usually disappears or will respond to the appropriate therapeutic measures, and digitalis may be discontinued. Auricular fibrillation almost always disappears with elimination of hyperthyroidism, although it may appear briefly postoperatively and disappear spontaneously. If it persists for more than two weeks after operation, it usually disappears after quinidinization (p. 279). If this is ineffective, the arrhythmia is probably due to independent cardiac disease and the patient should be digitalized to the desired point of slowing of the ventricular rate.

Hurxthal[36] reported an operative mortality rate of 4.3 per cent in 483 thyrocardiacs which was about five times as high as for uncomplicated Graves' disease. There is a recurrence of hyperthyroidism in about 10 per cent of cases, probably because of inadequate removal of thyroid tissue.[67, 37] Myxedema due to excessive removal of tissue, tetany due to accidental removal of the parathyroid glands and hoarseness or respiratory distress due to injury or ligation of the recurrent laryngeal nerve are among the operative complications.

Thiouracil, Methylthiouracil and Propylthiouracil. These antithyroid drugs, which inhibit the utilization of iodine to form the thyroid hormone,[39] have been used both to prepare the patient for operation and also for the prolonged, purely medical treatment of hyperthyroidism. Except for the exophthalmos and goiter they correct or eliminate virtually all of the symptoms of hyperthyroidism.

Thiouracil[3, 82, 9, 10] is given in doses of 0.4 to 0.6 gm. daily in divided doses, methylthiouracil[49, 84] in doses of 0.4 to 0.6 gm. daily and propylthiouracil[4, 30, 72] in doses of 0.2 to 0.3 gm. daily, with reduction of dosage when the desired effect is obtained. Thyroxin or desiccated thyroid is sometimes given simultaneously in order to prevent the thyrotropic effect of increased thyroid hyperplasia or exophthalmos during uracil therapy.[63]

Clinical improvement usually appears in two to six weeks, but a substantial reduction in the basal metabolic rate may require a longer period. If the thyroid gland is large or if iodine has been given in the previous six weeks, the effect of the uracils is delayed. Therapy may have to be continued for six months to a year or longer. In the majority of cases, the improvement obtained persists

when the drug is discontinued;[3, 82, 9] in the others there is a return of symptoms within a few months.

The chief toxic effect of the uracils is agranulocytosis, but this occurs much less frequently with propylthiouracil than with the other preparations. Blood counts must be done at weekly intervals. Prompt discontinuance of the drug if granulocytopenia develops, and the administration of penicillin almost always permit recovery from this complication. Other less serious toxic effects include fever, rashes, lymphadenopathy, joint pains, nausea and vomiting.[59] They usually disappear promptly after the drug is discontinued. Prolonged uracil therapy may produce myxedema, which may be disclosed by an elevated serum cholesterol before there is a significant reduction in the basal metabolic rate.

Radioactive Iodine. When radioactive iodine is given orally, the iodine is taken up rapidly and selectively by the thyroid secreting cells of the thyroid gland. There the contained radioactivity produces destructive effects similar to those of roentgen rays.[71] If a very small "tracer" dose of 100 microcuries of I^{131} is given to a person with a normal thyroid gland, about 30 to 60 per cent is excreted in the urine within forty-eight hours, the remainder being retained almost exclusively in the thyroid. In a patient with hyperthyroidism less than 20 per cent is excreted, for the hyperplastic gland takes up more iodine than the normal.[38, 55, 80a] The tracer dose may be used both as a diagnostic test and to determine the therapeutic dose of radio-iodine.

Hertz and Roberts[34] and Chapman and Evans[17] showed that hyperthyroidism could be controlled with a single dose of radio-iodine, as effectively as with subtotal thyroidectomy or the uracils. They employed a mixture containing chiefly I^{130} with a half-life of twelve hours. More recently I^{131} with a half-life of eight days (or a biologic half-life of six days to allow for excretion) has been employed in lesser dosage than was used by the above-mentioned investigators. The usual dose is about 8 to 12 millicuries of I^{131}, given once, by mouth, for a hyperthyroid patient with a gland estimated as weighing 40 to 60 gm. This dose tends to undertreat and may be followed if necessary by a second or even a third dose based on residual clinical findings. An interval of at least eight weeks should elapse between doses since 99 per cent of the radioactivity is dissipated in this period. The studies of Haines and associates[32] indicate that 200 microcuries of I^{131} per gram of thyroid tissue is an effective dose. In the thyrocardiac patient without palpable thyroid enlargement, the gland usually weighs about 40 gm. To obtain the necessary dose, allowance must be made for the percentage excreted in the urine as determined by the tracer dose. Inorganic iodine must not be given in the eight weeks prior to I^{131} because the gland may become saturated with the former and will not take up the radio-iodine. However, three days or more after the therapeutic dose of I^{131} has been given, compound solution of iodine may be given if the more rapid therapeutic effect of the latter is desired until the radio-iodine produces the more thorough and persistent result.

Clinical improvement usually is observed in about three weeks and the basal metabolism is reduced to normal in two to four months. A mild and transient myxedema may occur, and occasionally a more severe and persistent one, requiring small doses of thyroid.

In patients with thyrocardiac disease, auricular fibrillation and cardiac failure usually disappear without further treatment. If auricular fibrillation persists after the basal metabolism is reduced to normal, it usually responds rapidly to

quinidine even if it failed to respond prior to radio-iodine therapy. If not, the patient should be digitalized. Similarly heart failure responds satisfactorily to limitation of activity, digitalization, sodium restriction, diuretics, etc., even if it was refractory before the hyperthyroidism was controlled.

In a recent study[32] of 40 patients with exophthalmic goiter, consisting of severe cases recurring after thyroidectomy or associated with cardiac dysfunction, a single dose of I^{131}, averaging 242 microcuries per gram of estimated thyroid tissue, yielded good results in 27 cases, fair in 8 and poor in 5. Retreatment improved these results. Excellent results were also reported by Crile et al.[17a]

It seems highly probable that this promising form of treatment will replace both thyroidectomy and antithyroid drugs in the treatment of thyrocardiacs. The danger of producing thyroid carcinoma in later years is a theoretical risk, which should be taken in this group of patients.

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THE HEART AND CIRCULATION IN MYXEDEMA

Advanced myxedema is commonly associated with roentgenologic abnormalities in the cardiac silhouette and with electrocardiographic changes. Furthermore there is a strong suspicion that myxedema predisposes to coronary arteriosclerosis and its cardiac complications. But the existence of a specific form of myxedema heart disease which leads to heart failure is unproven.

Myxedema heart was first proposed as a clinical entity by Zondek,[69] who described diffuse enlargement of the heart, sluggish cardiac contraction and electrocardiographic abnormalities, all of which were reversible upon treatment with thyroid substance. These observations were confirmed without substantial change by Assmann,[4] by Meissner,[47] and in this country by Fahr,[19] Holzman,[32] Ayman et al.,[5] Lerman et al.,[38] Ohler and Abramson,[52] and McGavack and his associates,[43] among others. However, there is disagreement as to the nature and significance of the observed abnormalities.

The cardiac and circulatory changes to be noted are found only in cases of hypothyroidism in which the clinical picture of myxedema is fully developed. These patients have not only a very low basal metabolic rate (usually below minus 25) but also cold, dry, thickened and often edematous skin, loss of hair, and mental retardation. The cardiac and circulatory alterations associated with myxedema are not observed in cases of hypothyroidism without myxedematous skin changes and mental retardation, even when the basal metabolic rate is minus 20 or lower.[31]

The changes classified as "myxedema heart" are relatively rare since advanced myxedema is observed uncommonly. The incidence of cardiac abnormalities among cases of myxedema is variously reported from occasional to almost 100 per cent. According to Lerman, Clark and Means[38] myxedema heart as described by Zondek[69] occurred in 80 per cent of 48 adult cases of myxedema. Fahr[19] noted not only cardiac changes but evidences of cardiac failure in 75 per cent of 17 severe and moderately severe cases of myxedema. McGavack and his associates[43] also reported severe cardiac disturbances in 79 per cent of 24 cases of myxedema.

The so-called myxedema heart is observed with infantile as well as adult forms of myxedema.[7] Mussio-Fournier[49] observed the characteristic cardiac changes in 7 of 18 cases (38 per cent) of infantile myxedema. Among adults,

myxedema heart is associated with "spontaneous" myxedema, myxedema following thyroidectomy for hyperthyroidism, and myxedema induced by total thyroidectomy performed for the treatment of congestive heart failure or angina pectoris.

Age and Sex. Myxedema and "myxedema heart" are observed predominantly among women. They occur at all ages but in adults especially after the age of forty.

PATHOLOGY OF THE HEART

The scanty pathologic data thus far available provide insufficient evidence of a specific histologic cardiac lesion associated with myxedema. Schultz[57] described an homogenous infiltration, staining blue with hematoxylin, but differing in staining properties from the myxedematous infiltration occurring in the skin. Other non-specific changes have also been noted, including necrosis or degeneration of muscle fibers and replacement fibrosis.[11, 34] The muscle may appear grossly edematous,[44] and in the hearts of thyroidectomized animals edema has actually been demonstrated by measurement of the water content.[65]

Pericardial effusion, sometimes of considerable size (1000 cc.), has been demonstrated clinically[21] in autopsied cases[38] and in experimental hypothyroidism.[25, 65, 63] There is no evidence of associated pericarditis; thus the effusion represents an hydropericardium.

Dilatation and hypertrophy of the heart have been reported repeatedly, hypertrophy having been noted in 7 of the 20 autopsied cases collected by the Clinical Society of London.[54] However, there is no convincing evidence of true cardiac hypertrophy in myxedema uncomplicated by independent cardiac disease. A pseudohypertrophy, possibly due to edema, was noted grossly by Means.[44]

It is generally believed that arteriosclerosis develops earlier, and with greater frequency and intensity, in cases of myxedema than usual.[8] Fishberg[22] reported advanced arteriosclerosis in a boy of twenty-one with thyroid deficiency, and Willius[66] observed a myxedematous patient of twenty-three who succumbed to heart failure due to advanced coronary sclerosis and myocardial fibrosis, proven at autopsy. My own impression is that angina pectoris and coronary occlusion, which in the absence of hypertension and diabetes are confined almost exclusively to males, occur with unusual frequency in patients with myxedema, who are predominantly females. That is to say that myxedema, like diabetes and hypertension, predisposes the female to advanced coronary arteriosclerosis, which is otherwise rare in this sex. A relationship between myxedema and coronary arteriosclerosis is also supported by a number of reports of the production of arteriosclerosis in thyroidectomized animals.[18, 25] But the application of these experimental findings to human myxedema and coronary arteriosclerosis can only be considered with reservations.

PATHOLOGIC PHYSIOLOGY

Basal Metabolism and Oxygen Consumption. Myxedema is characterized by a *reduction in basal metabolism,* i.e., a diminution in the oxygen consumption of the tissues.[16] As a rule there is a reduction of 20 to 40 per cent below normal. Consequent to the diminished metabolism there is a sharp reduction in heat production. In contrast to patients with hyperthyroidism who experience

excessive heat production and uncomfortable sensitivity to warmth, patients with myxedema are unpleasantly sensitive to cold because of a deficient production of heat.

Peripheral Blood Flow. The peripheral blood flow was found to be diminished by Stewart and Evans[61] and by Abramson.[2] Corresponding to the diminished blood flow, the peripheral vascular channels are narrowed. Thus Zondek, Michael and Kaatz[70] found the capillaries of the nail bed extremely reduced in number and very narrow in caliber. There is an approximate linear relationship between the basal metabolism and peripheral blood flow. Instead of a normal blood flow to the skin of 4 per cent of the total cardiac output, only 1.3 per cent of the cardiac output was allotted to the skin in patients with an average basal metabolic rate of minus 30.[61] By contrast, in patients with hyperthyroidism, 6 per cent of the total cardiac output is apportioned to the skin.

The diminished peripheral blood flow in myxedema probably results from the diminished production of vasodilating metabolites and from the tendency to cooling of the blood because of the low heat production. Both of these factors tend to cause peripheral vasoconstriction and diminished blood flow. Clinically they produce the cool dry skin of myxedema, which contrasts with the warm moist skin of hyperthyroid patients.

The circulatory disturbances of myxedema may be viewed as compensatory mechanisms whereby the body adjusts to the reduced need of the tissues for oxygen, and whereby the body maintains its normal stable temperature despite a diminished production of heat. Reductions in peripheral blood flow, venous return, cardiac output, work of the heart and blood volume all denote readjustments to the lowered level of tissue metabolism. At the same time the need for heat conservation (because of the diminished heat production) appears to be satisfied both by the narrowing of cutaneous vessels and by the heat-retaining properties of the edematous infiltration of the skin in myxedema. The mechanism responsible for the myxedematous infiltration is obscure. Low cellular metabolism, slowing of the blood stream, diminished blood flow to the skin and increased capillary permeability are among the possible causative factors. The existence of increased capillary permeability in myxedema was demonstrated by studies with the dermofluorometer.[35] By the same method capillary permeability was found to be unaltered in patients with cardiac edema.

Venous Return and Minute Volume (Cardiac Output). The diminished peripheral blood flow results in a *reduction of the venous return* to the heart and this in turn is reflected by a *fall in the minute volume* (cardiac output).[6, 3, 28, 60] According to the observations of Stewart et al. the cardiac output in cases of myxedema averaged 1.17 liters per minute per square meter of body surface before treatment and 1.98 liters after adequate treatment with thyroid. It is noteworthy that whereas the cardiac output was 60 per cent of normal the proportion supplying the skin was only 25 per cent of normal. This indicates that there is a relatively greater reduction of the cardiac output going to the skin in myxedema than to other organs, another example of the mechanism of heat conservation in this disease.

Although the available data are inconclusive, they suggest that the reduction in cardiac output is due both to a retarded heart rate and to a fall in the stroke output. This association of bradycardia and a low stroke output is unusual in that slowing of the heart rate usually permits greater ventricular filling and is therefore associated with an increased output per beat.

The *arteriovenous difference* is increased in cases of myxedema[60] due to slowing of the peripheral blood stream which permits greater oxygen utilization by the tissues. This reduces the load on the heart; consequently, the cardiac output and work of the heart in myxedema are diminished to a greater degree than is the oxygen consumption. Since the efficiency of the heart is greater the less work it performs for a given amount of body metabolism, the heart in myxedema is more efficient than normally. Briard and his associates[13] demonstrated a very efficient conversion of calories into kg. meters of work as compared to the response of the heart in hyperthyroidism. In fact, 19 per cent less energy was utilized by myxedematous patients in walking than by normal subjects. The mechanisms described for conserving heat probably account for the improved efficiency in myxedema. In hyperthyroidism the cardiac output and work of the heart are increased even more than the oxygen consumption, i.e., cardiac efficiency is diminished, probably because of the energy wasted in the dissipation of excessive heat.

Heart Rate. Bradycardia is a frequent finding in advanced myxedema. The pulse rate frequently ranges between 50 and 70 in the absence of conduction disturbances. The mechanism of the slow pulse rate is uncertain, although it may represent a reverse of the Bainbridge reflex due to the slow and diminished venous return (contrast with hyperthyroidism, p. 914).

Blood Pressure and Pulse Pressure. The blood pressure shows no constant or significant change. Both the systolic and diastolic pressures may be low and the pulse pressure may be small, presumably because of the sluggish circulation and cardiac action. An elevation of the blood pressure and the pulse pressure may follow the administration of thyroid substance. Occasionally hypertension is associated, probably fortuitously. But in some cases the youth of the patient[22] and the fall in blood pressure after the administration of thyroid[17, 52] suggest a possible relationship between the hypertension and the myxedema.

Velocity of Blood Flow. Circulation Time. Venous Pressure. The blood flow is significantly slowed in proportion to the degree of reduction in basal metabolism and the slowing of the peripheral blood flow.[12, 41, 60, 43] The circulation time from arm to tongue is frequently between 20 and 30 seconds, compared to a normal of between 9 and 16 seconds.

The *venous pressure* is usually normal.[36, 60] However, Mussio-Fournier and his associates[50] reported an elevation in venous pressure in at least 6 of 12 cases of myxedema heart disease. But these observers could find no relationship between the venous pressure as they determined it and the presence or absence of heart failure. Careful determinations of the venous pressure should help to decide whether the serous effusions and edema are evidences of heart failure or of myxedema.

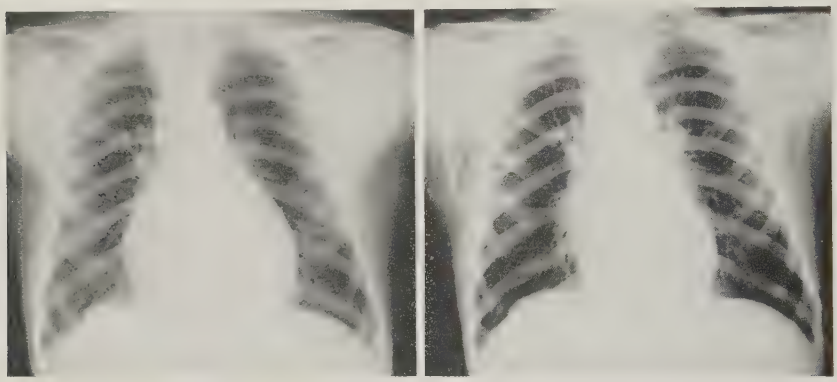
Blood Volume. The *circulating blood volume* was found to be diminished by Thompson[64] and by Gibson and Harris.[24, 59a] This may be a consequence of reduction in the peripheral vascular bed and represents an adjustment to the lessened need for supplying oxygen to the tissues. In terms of the low metabolic needs the cardiac output, although diminished, is adequate. Furthermore, the peripheral vasoconstriction causes a favorable redistribution of the cardiac output to the brain, heart and internal organs and a less than normal blood volume suffices to maintain the functions of the circulation.

Vital Capacity. The *vital capacity* is significantly diminished,[62, 37, 12, 28] in spite of the absence of pulmonary congestion. The vital capacity in myxedema

is similar to that in hyperthyroidism, whereas most of the circulatory disturbances in these two conditions provide distinct contrast. This may be explained by the fact that the reduced vital capacity both in hyperthyroidism and myxedema is unrelated to the circulatory disturbances. In myxedema the vital capacity may be diminished because of reduction in the metabolism and work of the muscles of respiration, while in hyperthyroidism these muscles may be impaired by a disturbance in creatine metabolism (p. 918). Furthermore the vital capacity in myxedema may be reduced by the frequently associated elevation of the diaphragm and occasionally by the presence of pleural effusions. It should be noted that there is disagreement as to the vital capacity in myxedema, for Schnitker, van Raalte and Cutler[55] failed to observe a reduction in vital capacity in cases of hypothyroidism following thyroidectomy.

CLINICAL FEATURES OF THE HEART

Subjective symptoms referable to the heart are relatively uncommon and consist of angina pectoris or complaints due to congestive heart failure.



A B

Fig. 77. Heart in myxedema. *A*, Generalized enlargement of the heart when B.M.R. was — 50 per cent.
B, After two months of treatment with thyroid.

Objective findings are more frequent and more characteristic and include enlargement of the heart, sluggish cardiac action, electrocardiographic changes and signs suggesting congestive heart failure.

Cardiac Enlargement. The heart is definitely enlarged in most cases of advanced myxedema. This may be ascertained by percussion or more readily by roentgen ray examination. The enlargement, which extends both to the left and the right, gives the cardiovascular silhouette a ham-shaped configuration (Fig. 77). There is a close resemblance to the roentgenologic appearance of pericardial effusion. In 34 of 48 cases of myxedema, Lerman, Clark and Means[38] observed cardiac enlargement as denoted by a transverse diameter which exceeded half the diameter of the chest by 1 cm. or more; in 22 of these the transverse diameter of the heart exceeded half the diameter of the chest by 5 cm. or more.

Thyroid hormone specifically reduces the size of the heart (Fig. 77); withdrawal of the thyroid is followed by enlargement to its previous size.[69, 19, 45] After three to four weeks of treatment there is a noticeable shrinkage of the

cardiac shadow, but complete restoration to normal size may require continuous treatment for at least six weeks and sometimes for three to four months. The rapid development and reversibility of the cardiac enlargement in myxedema suggests that there is no true hypertrophy of the myocardial fibers.

The cause of the cardiac enlargement is uncertain. The absence of specific pathologic changes in the heart has been discussed (p. 931). The enlargement may be due chiefly or partially to myxedematous infiltration or interstitial edema similar to that occurring in the skin and subcutaneous tissue.[44] Evidence of increased permeability of the capillaries tends to support this explanation.[35]

Enlargement of the cardiac silhouette has been attributed to an associated *pericardial effusion* rather than to dilatation or hypertrophy of the heart itself.[56] In fact the similarity of the roentgenologic appearance of the heart in myxedema and of that of pericardial effusion has already been noted (p. 934). Pericardial effusions of considerable size have been aspirated repeatedly during life[27, 23, 42, 21] and have been noted also at autopsy.[38] The findings at postmortem examination are usually obscured by the effects of thyroid administered during life. Furthermore, pericardial aspiration has been performed in a relatively small number of cases; even when fluid is obtained it is not always sufficient to explain the degree of cardiac enlargement.[33] But recently Kern et al.[33a], by means of pericardial taps in 4 successive cases, provided strong evidence that pericardial effusion is a constant and major factor in the cardiac enlargement and other features of myxedema heart.

According to Fahr,[19] the cardiac enlargement observed clinically and roentgenologically may represent true cardiac dilatation. This concept assumes that the myxedema heart is hypodynamic and its contractility impaired,[28] i.e., the efficiency of the heart is less than normal and therefore it dilates in order to perform the same mechanical work as the normal heart. This interpretation is contrary to many principles of circulatory physiology. Actually the heart in myxedema is as efficient or more efficient than normal because its cardiac output and work performed are diminished proportionally more than the reduction in oxygen consumption of the tissues (p. 933). Ordinarily cardiac dilatation is a successful compensation and is associated for a long time with a normal or only slightly abated cardiac output. When the output wanes significantly, the blood volume increases. Although the heart is enlarged in myxedema, the cardiac output is sharply diminished and the blood volume is significantly below normal. Therefore there is in fact little or no evidence to assume that the enlarged cardiac shadow in myxedema represents a compensatory dilatation to offset a diminishing cardiac output. In the present state of knowledge, it appears most probable that the enlargement is due partially to myxedematous infiltration or interstitial edema similar to that in the skin, and that pericardial effusion may contribute in varying degree to enlargement of the cardiac silhouette.

Sluggish Cardiac Action. Physical and roentgenologic examination of the heart in myxedema discloses a sluggish action which contrasts with the dynamic hyperactivity of the heart in Graves' disease.

On physical examination it is usually difficult or impossible to feel a precordial pulsation or to localize the apical impulse. The heart sounds are soft and distant.

Fluoroscopic examination discloses sluggish cardiac contractions, wormlike in character and of minimal amplitude. This is remarkable because of an

associated bradycardia, which usually consorts with strong cardiac pulsations. The pulse is extremely small and the rate slowed to 50 to 70 per minute.

Cardiac Failure. There is considerable disagreement as to the incidence of congestive heart failure in patients with myxedema. It is questionable whether it ever occurs independently of associated intrinsic cardiac disease such as coronary arteriosclerosis with myocardial infarcts. According to Fahr,[19] symptoms and signs of heart failure were present in 13 of 17 cases, i. e., in 75 per cent, and in 5 of them these manifestations were severe. All of the patients presented dyspnea, râles at the bases of the lungs and pitting edema. Similarly, McGavack and his associates[43] observed 24 patients with frank myxedema, of whom 19 exhibited evidence of severe heart failure. But other etiologic factors could not be excluded since 1 patient had syphilitic aortitis, 13 had "arteriosclerotic changes" and 5 had hypertension. On the other hand, many observers have never witnessed congestive heart failure in association with myxedema, or have been able to attribute it to independent etiologic forms of heart disease.[67, 38]

There are undoubtedly many symptoms and signs associated with advanced myxedema which are similar to those of congestive heart failure, but their pathogenesis is probably different. Thus peripheral edema and serous effusions (ascites, pleural effusions and hydropericardium) may occur in myxedema as in heart failure. But their origin in the former is probably due to increased capillary permeability,[35] while the edema and serous effusions of heart failure are associated with little or no change in capillary permeability. This explanation is supported by the finding of relatively high protein content in the pericardial and other serous effusions in myxedema.[29, 50] Hypoproteinemia occurs occasionally with myxedema, but it is less common than in cases of advanced congestive heart failure in which there is widespread anasarca. The venous pressure is usually normal and the blood volume reduced in myxedema, while in advanced heart failure (as denoted by widespread anasarca) the venous pressure and blood volume are significantly increased. Fluoroscopic examination shows no pulmonary congestion in myxedema with cardiac enlargement and serous effusions, while such congestion is common in congestive heart failure. Finally the peripheral "edema" and serous effusions of myxedema do not respond to digitalis or diuretics as do similar manifestations of congestive heart failure. In summary, there are many reasons for concluding that the manifestations of myxedema which simulate those of myocardial insufficiency are actually unrelated to failure of the heart. This does not contradict the occasional occurrence of true heart failure as a result of an associated independent cardiac disease.

Angina Pectoris and Coronary Occlusion. The association of angina pectoris with myxedema was noted by Hertoghe[30] and by Zondek,[69] and more recently was reviewed by Peel.[53] The angina pectoris is probably due to severe coronary arteriosclerosis to which myxedema predisposes. Bartels and Bell[8] reported that among 59 patients beyond the age of twenty with spontaneous myxedema, 15 presented clinical evidence of coronary artery disease. Sturgis[62] suggested also that the anemia frequently found in myxedema may be a contributory factor. Most frequently the angina pectoris appears only after the institution of thyroid therapy and the elevation of the basal metabolic rate, as noted by Abrami, Brule and Hietz,[1] Means, White and Krantz,[46] and by Christian.[14] In

these cases also it is probable that the angina pectoris was due to coronary arteriosclerosis, but myocardial anoxia sufficient to cause pain did not develop until the work of the heart was increased by thyroid therapy. Patients relieved of angina pectoris by total thyroidectomy may suffer a recurrence of the pain if thyroid is administered.

A more obscure group is formed by the cases in which angina pectoris associated with myxedema is reported to have improved following treatment with thyroid. Such cases have been documented by Laubry, Mussio-Fournier and Walzer,[36] Ziskin,[68] Beach,[9] and by Beaumont and Robertson.[10] A satisfactory explanation for the mechanism by which thyroid therapy could relieve angina pectoris has not been submitted. The descriptions of the angina pectoris in the reported cases are quite meager and one may question whether these patients suffered from angina pectoris or from chest pain of noncardiac origin. In the case reported by Beaumont and Robertson the correlation between relief and thyroid therapy is not convincing; furthermore, the reported electrocardiographic changes suggest that relief of the paroxysms followed the occurrence of myocardial infarction.

Although there are no satisfactory statistical data, I have the distinct impression from my own experience and that reported by others that coronary thrombosis and myocardial infarction occur with unusual frequency in patients with myxedema. Very few autopsy reports are available, but in those recorded in recent years, coronary occlusion and myocardial infarction appear common. In the single autopsied case described by Fahr[20] there was an arteriosclerotic coronary occlusion with necrosis of the myocardium. In the only 2 cases of Higgins[31] in which autopsies were obtained, old or recent coronary occlusion and myocardial infarction were present in both. Similarly there was an acute coronary occlusion in the autopsied case reported by Means and Lerman[45] and in that reported by Smythe.[59]

The occurrence of angina pectoris and coronary thrombosis in myxedema is all the more remarkable because myxedema is essentially a disease of females, while angina pectoris and coronary thrombosis occur predominantly in males. It is probable that myxedema, like diabetes and hypertension, by predisposing to coronary arteriosclerosis neutralizes the usual predominance of males in cases of angina pectoris and coronary occlusion.

Electrocardiographic Changes. The electrocardiographic changes represent a cardinal feature of the myxedema heart as described by Zondek.[69] These changes consist of (1) low voltage of all the complexes, but most frequently of T and P, (2) flattening or inversion of the T waves, (3) restoration of upright T wave and increased voltage of the ventricular complexes following thyroid therapy.

The most constant feature is the flattening or inversion of the T waves, especially in leads I and II. These may become upright following the administration of potassium salts.[58] The P waves may also be almost flat or absent in one or more leads.

The P-R interval is frequently at the upper limit of normal and occasionally it is prolonged to as much as 0.4 seconds.[52, 68] Partial heart block, which improved after thyroid therapy, was reported by Willius,[66] Luten,[40] Fahr[19] and others. In such cases the heart block has been attributed to myxedematous infiltration of the bundle of His or to increased vagal tone. On the other hand

an excessive P-R interval may persist or become prolonged despite thyroid medication. This usually denotes that the heart block is caused by independent cardiac disease (due to coronary arteriosclerosis), for there are often associated intraventricular conduction disturbances and negative T waves which likewise persist despite specific therapy.

Sometimes the QRS complex is notched, widened and of low voltage in the absence of a prolonged P-R interval. This also suggests the presence of independent myocardial disease. As a rule the QRS complex is more likely to remain unaltered in myxedema than the P or T waves. The salient feature of the electrocardiographic changes due to myxedema is their correction by adequate and prolonged thyroid medication. Within three weeks there is an increase in voltage, the T waves if inverted become upright and the P waves reappear or become taller.

The cause of the characteristic electrocardiographic abnormalities is uncertain, but their rapid regression following thyroid therapy indicates a direct relationship to the myxedema itself. Poor conductivity (i. e., increased electrical resistance) resulting from the thickened edematous skin[51, 39] is not the cause since identical tracings are obtained by direct needle electrodes that pierce the skin[15] or are inserted into veins in the extremities.[49] The similarity to the electrocardiogram associated with pericardial effusion suggests that the changes observed with myxedema are actually due to a concomitant pericardial effusion.[56] But the association of a significant pericardial effusion in all cases of myxedema with typical electrocardiograms, and the regular disappearance of the electrocardiographic abnormalities after pericardial paracentesis, are unproven. The low voltage of the auricular and ventricular complexes may actually mirror weak action currents associated with the sluggish cardiac contraction in myxedema. A variety of other explanations[28] relating the electrocardiographic changes to vagotonia, low basal metabolism,[48] associated anemia, and myocardial anoxia have been offered without conclusive or consistent evidence.

DIAGNOSIS AND PROGNOSIS

The presence of myxedema should be recognized from the characteristic cold, dry, thickened skin, scanty hair and eyebrows, puffy eyelids, mental and physical sluggishness, constipation and intolerance to cold. In the cases associated with cardiac and circulatory changes, the basal metabolic rate is usually between minus 25 and minus 35 per cent. The presence of "myxedema heart" is denoted by significant cardiac enlargement to the left and the right, and by the low voltage and flattening and inversion of the T waves in the electrocardiogram in patients with the above-mentioned evidences of myxedema. Diagnostic confirmation is obtained by the reduction in the size of the heart, the restoration of a normal electrocardiogram, and other evidences of clinical improvement following thyroid therapy.

Occasionally, when other signs of myxedema are overlooked, the possibility of this condition should be considered when there is (1) unexplained cardiac enlargement, (2) clinical or roentgenologic evidence of pericardial effusion, (3) flattening or inversion of the T waves, or (4) diffuse anasarca without evidence of hypertension, rheumatic cardiovalvular disease or coronary arteriosclerosis. The therapeutic effect of thyroid should be observed whenever there is doubt

as to the possible myxedematous origin of these abnormalities. In making a diagnosis of myxedema with cardiac changes, one should constantly bear in mind the frequency of coexistent coronary arteriosclerosis and its cardiac consequences.

TREATMENT

Thyroid substance or thyroxin is the specific treatment for myxedema, with or without cardiac and circulatory abnormalities. The important point to remember is that the thyroid must be administered cautiously and in small dosage because of the danger of precipitating angina pectoris and, more seriously, heart failure, especially acute left ventricular failure.[43] Satisfactory initial doses range from 1/20 to 1 grain of thyroid substance daily. Ultimately stabilization can usually be attained by doses of 30 to 180 mg. (½ grain to 3 grains) daily. This applies to preparations containing 0.2 per cent iodine according to U.S.P. standards. Since various preparations may differ in potency, the dosage should be adjusted accordingly.

As a rule it is safe to begin with 8 mg. (⅛ grain) of thyroid daily and to increase it gradually by increments of 8 mg. according to the clinical response. If possible, the patient should be ambulant in order to observe the effect of activity. Four to eight weeks are usually required to obtain a satisfactory result. If angina pectoris develops, it may be necessary to maintain the patient at slightly hypothyroid levels. With satisfactory treatment there is a striking diminution in the size of the heart, increase in voltage of the ventricular complex in the electrocardiogram, more forceful cardiac activity, increase in the cardiac output and volume, heart rate and rate of circulation as well as an elevation in the basal metabolic rate and a regression of serous effusion and other evidences of myxedema. McGavick et al.[43] found that a decrease from the initially high permeability was one of the earliest and most constant signs of improvement. Loss of weight and a fall in blood cholesterol are other early objective signs of improvement.

It is questionable whether the repeatedly emphasized risk of too rapid or excessive thyroid therapy applies to the ordinary cases of so-called "myxedema heart" in which there is enlargement, etc., but no associated severe coronary arteriosclerosis. For as the metabolism increases, the capacity and work of the heart increase pari passu. There is danger only in the presence of severe coronary arteriosclerosis. For then the increased metabolism and increased cardiac work after thyroid medication may result in relative myocardial anoxia (coronary insufficiency), myocardial necrosis (if the anoxia is severe and protracted), or heart failure (if the heart was already previously damaged by myocardial infarction).

Digitalis is of no benefit and is not indicated for the treatment of the cardiac and circulatory changes due to myxedema alone. Occasionally it may be difficult to distinguish whether some of the symptoms and signs represent congestive heart failure or the consequences of myxedema alone. In such cases the myxedema should first be controlled by thyroid administration. After adequate treatment, it may be apparent that there are residual symptoms which must be interpreted as those of congestive heart failure, usually due to coronary arteriosclerosis. In such cases, digitalis and other measures directed toward the control of heart failure (Chapter 9) should be instituted.

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42

OTHER ENDOCRINE, METABOLIC AND NUTRITIONAL DISTURBANCES

THE PITUITARY

Pathologic Physiology

The posterior lobe of the pituitary gland produces at least two hormones: (1) a vasopressor and antidiuretic and (2) an oxytocic which causes uterine contraction. The antidiuretic hormone, by its control of renal excretion, is important in water balance. Nevertheless, deficiency of this hormone in diabetes insipidus is not associated with distinctive pathologic effects on the heart or circulation. Little is known regarding possible abnormal excess of this hormone.

The anterior lobe of the pituitary produces hormones which influence growth and development, reproduction and metabolism. It controls or modifies the action of the thyroid, adrenals, gonads and other endocrine glands by its thyrotropic, adrenotropic, gonadotropic hormones. Directly or through its effects on other glands, it has a profound influence on carbohydrate, fat and protein metabolism, as well as on salt and water metabolism.

It is conceivable that the most important effects of the pituitary gland on the development of cardiovascular disease are still unknown. Through its influence on fat and protein metabolism it may be concerned with the pathologic lipid alterations in coronary atherosclerosis. Selye and his associates[9] have described the occurrence of renal arteriosclerosis and myocardial fibrosis following injections of anterior pituitary extracts in rats but these observations may not be transferable to human pathology. A relation of the anterior pituitary to edema has been suggested because of the occurrence of premenstrual edema[14] and of edema in the toxemia of pregnancy.[4] These may be adrenotropic or gonadotropic effects. More definite relationships to cardiovascular pathology are found in the specific diseases or syndromes resulting from hyperfunction or hypofunction of the anterior pituitary gland. The preliminary report of beneficial effects of cortisone (compound E) and pituitary adrenocorticotropic hormone (ACTH) on rheumatic fever may open a new field for investigation of the pituitary-adrenal relationships to cardiovascular disease.[9a]

Hyperfunction of the Anterior Pituitary. Acromegaly

The anterior lobe of the pituitary is composed of eosinophilic (acidophilic), basophilic and chromophobe cells. Adenoma of the eosinophilic cells or hyper-

function of these cells results in gigantism before puberty and acromegaly in adults.

Acromegaly is characterized by enlargement of the skull, mandibles and the terminal parts, the adjacent soft tissues and in fact all the viscera. With respect to the heart, the most impressive finding is a pronounced *cardiac hypertrophy* exceeding that to be anticipated from the generalized splanchnomegaly.[10, 13] The weight of the heart commonly exceeds 500 gm.[3] Occasionally the weight of the heart ranges approximately between 1000 and 1300 gm.[12, 5, 3] A second finding, which is stressed less often, is the common occurrence of advanced arteriosclerosis, notably *coronary* atherosclerosis. Cardiac abnormalities are not associated with gigantism unless acromegaly is also present.

The pathogenesis of the association of arteriosclerosis and cardiac hypertrophy to acromegaly is uncertain. The common occurrence of diabetes in acromegaly[2] (adrenotropic or pituitary diabetogenic hormone) is worthy of attention in view of the striking association of diabetes with premature and advanced coronary atherosclerosis (p. 951). Hyperthyroidism, which accompanies acromegaly frequently, has been given as a cause for the cardiac hypertrophy, but this relationship may be questioned (p. 917).

It is more probable that the excessive cardiac hypertrophy results from the hypertension and from progressive heart failure due to hypertensive and arteriosclerotic heart disease. Hypertension was found frequently in the 21 cases analyzed by Bartelheimer[1] and was attributed to concomitant hyperfunction of the basophile portion of the anterior pituitary lobe. The occurrence of heart failure was stressed in the collection of 25 cases of acromegaly recorded by Fournier.[8] Heart failure and hypertension were observed in the patient studied by Humphry and Dixon,[11] whose heart subsequently was found to weigh more than 1100 gm. Similarly the remarkable cardiac enlargement in Zondek's[15] case could be explained by the blood pressure of 210/140 and by the dyspnea and cyanosis indicative of cardiac insufficiency. Courville and Mason[3] reported that pronounced heart failure was present in 18 (75 per cent) of their patients with acromegaly. Weakness, attacks of syncope, breathlessness and anasarca were the outstanding manifestations, often in contrast with the false appearance of physical strength presented by these individuals. The electrocardiogram disclosed left axis deviation, widening and slurring of the QRS and occasionally T wave changes, late in the disease. Bartelheimer[1] found electrocardiographic evidence of myocardial damage in 14 of 21 cases of acromegaly.

Basophilism—Cushing's Syndrome

See Hyperfunction of Adrenal Cortex below.

Pituitary Insufficiency—Simmonds' Disease

Severe hypofunction, atrophy or destruction of the anterior pituitary by tumors, cysts or infarcts is associated with generalized atrophy of the other endocrine glands (adrenals, thyroid and gonads) as well as of all the bodily organs.[7] With respect to the heart, the effects of pituitary insufficiency may be similar to those described under myxedema (p. 930), or more strikingly to those described under Addison's disease (p. 946). The heart participates in the generalized atrophy of the various organs. Microscopic examination may disclose brown atrophy of the heart and degeneration of the muscle fibers.

The electrocardiogram shows very low voltage of the QRS complexes and low, flat or diphasic T waves in standard leads.[6]

THE ADRENAL GLANDS

Pathologic Physiology

The adrenal glands are composed of two functionally different portions, the cortex, which is essential to life, and the medulla, which is part of the chromaffin system. The latter includes also similar tissue found in the sympathetic ganglia and carotid bodies.

The adrenal cortex produces a variety of chemical substances termed steroids, several of which are physiologically potent. The most important function of these hormones is the control of salt and water metabolism. However, the adrenal cortex also influences carbohydrate metabolism and probably also the metabolism of proteins. Aside from the cardiovascular effects to be noted under the individual adrenal diseases, it is probable that the adrenal cortex is concerned with the control or modification of water balance in heart failure, perhaps by action on the kidney or the intercellular tissues. Some of the important influences attributed to the anterior pituitary gland may be mediated through the adrenal cortex. In the previously quoted experiments in which Selye et al.[9] produced cardiac fibrosis and renal arteriosclerosis in rats by injection of anterior pituitary extract, these effects failed to develop if the adrenal cortex was previously removed.[30]

The adrenal medulla produces the hormone epinephrine (adrenaline) which has widespread circulatory as well as metabolic effects through its sympathomimetic action. In various emergency states, including shock, the outpouring of epinephrine serves to effect important circulatory adjustments. The secretion of epinephrine secondarily stimulates secretion of the adrenotropic hormone.[34] Excessive secretion due to medullary tumor (pheochromocytoma) produces a distinctive clinical picture with cardiovascular manifestations (see below).

Hyperfunction of the Adrenal Cortex

Hyperfunction of the adrenal cortex, usually due to benign or malignant neoplasms, may cause the adrenogenital syndrome or Cushing's syndrome. The former is characterized by sexual precocity, hermaphroditism, virilism of females or feminization in males, loss of libido, etc. These cases, in pure form, are not associated with distinctive cardiovascular manifestations.

Cushing's syndrome occurs chiefly in women and is characterized by obesity, especially of the trunk, neck, and face (moon face), hirsutism, amenorrhea and loss of libido, bluish abdominal striae, hypertension, hyperglycemia and tendency to glycosuria, hypercholesterolemia, osteoporosis, especially of the spine (kyphosis), and polycythemia. Many of these features are obviously similar to the effects of stimulation of the anterior pituitary gland. In fact, Cushing[21] found a basophilic adenoma in some cases while in the remainder hypersecretion of the basophilic cells (basophilism) was assumed. It is now well known that tumors of the adrenal cortex produce the identical syndrome and it is highly probable that even in cases of basophilic pituitary tumor the syndrome results from overstimulation of the adrenal cortex by the

pituitary adrenotropic hormone.[54, 16] Rarely Cushing's syndrome has been associated with tumors of the thymus (p. 950).

The most important findings with respect to the heart are hypertension, which may be of intense degree, and associated cardiac hypertrophy. Renal insufficiency and death from a cerebral accident may result from malignant hypertension.[47, 36] In a case which I observed and which was studied and reported by Oppenheimer and Silver,[40] there was malignant hypertension, severe hypertensive neuroretinitis, renal insufficiency (azotemia) and hyperglycemia. Eventually death resulted from congestive heart failure.

Glycosuria, diminished glucose tolerance or frank diabetes is observed in many cases of Cushing's syndrome.[51] This association of diabetes and hypertension, noted previously in connection with acromegaly, is of interest because it is commonly found in combination with severe coronary arteriosclerosis in cases not due to apparent endocrinopathy. These relationships suggest the possibility that hypertension, diabetes and coronary atherosclerosis are not haphazard associates but the result of some common endocrine metabolic factor.

The hypertension observed in patients with Cushing's syndrome due to adrenal cortical tumors is probably due to an hypertensive factor secreted by the adrenal cortex. This belief is supported by the observation that the synthetic steroid desoxycorticosterone produces a progressive and sometimes alarming increase of blood pressure in patients with adrenal insufficiency (Addison's disease),[25, 45] as well as a less pronounced elevation of blood pressure in normal man.[42] The administration of excessive amounts of desoxycorticosterone to patients with Addison's disease is followed not only by hypertension, but also by subcutaneous edema and other signs of congestive heart failure, such as gallop rhythm, enlargement of the heart, increased venous pressure and roentgenologic evidence of pulmonary congestion.[25, 24, 39, 52, 56, 20] It is probable that these manifestations are the consequence of excessive salt and water retention and increase in blood volume due to the effect of desoxycorticosterone on renal excretion of sodium. I have also observed the development of angina pectoris, simultaneously with hypertension and peripheral edema, in a man with Addison's disease who received an excessive amount of desoxycorticosterone from implanted pellets of this substance.

Electrocardiographic changes involving the T wave were noted by Raab[43] after giving desoxycorticosterone to normal men, but these changes were not striking. Currens and White[20] described much more pronounced abnormalities when excessive amounts of this substance and sodium chloride were administered to patients with Addison's disease. There was a progressive diminution in the voltage of the QRS and T waves and subsequent isoelectric or inverted T waves in leads I and II. These patients also developed congestive heart failure. Currens and White called attention to the similarity in T wave changes to those described as being due to diminished serum potassium in cases of familial periodic paralysis.[53] This possible relationship of cardiac changes in Addison's disease to potassium deficit is discussed below (p. 947).

Hyperfunction of the Adrenal Medulla—Pheochromocytoma, Paraganglioma

Tumors of the chromaphil tissue of the adrenal medulla (pheochromocytoma) or of the extra-adrenal chromaphil cells in the sympathetic paraganglia

and carotid bodies (paraganglioma) produce excessive amounts of epinephrine which is constantly or paroxysmally secreted into the blood stream.[18] Epinephrine in crystalline form has been recovered from these tumors.

The clinical manifestations of these tumors, often alarming in severity, are those to be anticipated from the vasopressor effects of injecting large doses of epinephrine. Patients with pheochromocytoma or paraganglioma usually exhibit paroxysms (minutes or hours) of severe hypertension (200 to 300 mm. Hg), anxiety and tremulousness, cardiac pain, palpitation with tachycardia, dyspnea, headache and nausea or vomiting, glycosuria and pronounced vasomotor phenomena including pallor or flushing and sweating.[37, 31, 35, 17] Attacks of acute pulmonary edema occur in about half the cases. Electrocardiographic changes may appear during the paroxysm, e.g., auricular fibrillation, deformed ventricular complexes and atrioventricular dissociation.[23] Death may result from an acute coronary occlusion or a cerebral accident.

Of particular interest are the cases in which the hypertension associated with pheochromocytoma is not paroxysmal in occurrence but persistent and severe.[41, 57] These cases may simulate and be mistaken for cases of essential hypertension of the so-called malignant type. Persistent hypertension due to pheochromocytoma or repeated paroxysms over a long period may be associated with vascular changes in the fundus, cardiac enlargement and renal insufficiency.

It is important to recognize such cases because of the possibility of successful excision of the causative tumor with cure of the clinical symptoms, including regression of the fundal, cardiovascular and renal abnormalities.[19, 32]

The diagnosis may be made readily if the physician is familiar with the clinical picture and sees the patient during an attack. Between attacks, the diagnosis may be suggested by the history of the paroxysms if the physician is mindful of the condition. Confirmation may be found in the demonstration of a tumor shadow in the adrenal region by ordinary roentgenologic examination or after perirenal insufflation with oxygen. A mass may be palpable in the renal region and its manipulation may precipitate an attack. The administration of histamine[44] or of mecholyl[29] may cause an excessive release of epinephrine and this has been recommended as a possible test for pheochromocytoma.[44] Goldenberg et al.[27] employed the adrenolytic benzodioxane (933F), which caused a sharp fall in both systolic and diastolic pressure in cases of pheochromocytoma, but not in cases of essential hypertension. In cases of persistent, severe hypertension there may be also a history of previous paroxysms. If a sympathectomy is performed for severe hypertension, the adrenals should be inspected for the presence of a tumor.

Hypofunction of the Adrenal Cortex—Adrenal Insufficiency—Addison's Disease

Addison's disease, in which severe adrenal insufficiency results from tuberculosis or diffuse atrophy of the adrenal cortex, is characterized by profound asthenia, striking hypotension, brown pigmentation and by acute crises which are dominated by nausea and vomiting, dehydration, fever and shock due to loss of sodium and water.

The profound weakness overshadows any cardiac symptoms in the chronic untreated state but dyspnea and palpitation are common. These symptoms are mitigated by the limited activity which the patient's asthenia permits.

Hypotension is characteristic during the chronic and acute phases and is the most constant cardiovascular manifestation. The blood pressure is usually below 100 mm. Hg and often between 80 and 90. The diastolic pressure is usually between 60 and 70 mm. Hg and the pulse pressure is low. During a crisis, the systolic pressure falls below 80 and often to such low levels that it is unobtainable. The fall in blood pressure is due to deficiency of adrenal cortical hormone and not to lack of medullary epinephrine, for the blood pressure can be restored to normal or even hypertensive levels by the administration of sodium chloride and desoxycorticosterone (p. 945). The occurrence of frank evidences of congestive heart failure in patients with Addison's disease, following excessive desoxycorticosterone therapy, has also been discussed (p. 945).

The heart in Addison's disease, as in anterior pituitary insufficiency, is small in size and shows poor filling (i.e., it is hypodynamic) on fluoroscopic examination. To some extent the smallness of the heart parallels the severity of the disease and conversely the cardiac silhouette enlarges following treatment with sodium and desoxycorticosterone.[38, 39] In fact, the varying size of the heart has been utilized as a guide to treatment with desoxycorticosterone, for according to McGavack[39] an abnormally large cardiac silhouette on teleoroentgenograms was the first and most reliable sign of excessive dosage. The small size of the heart in Addison's disease is probably due chiefly to the reduction in blood volume, i.e., to the proportionally small volume of blood in the cardiac chambers and the consequently low diastolic tension. However, the loss of potassium and water from heart muscle as well as other muscular tissue[59] has also been cited as a factor in diminishing the size of the heart.

The electrocardiogram of Addison's disease often discloses low voltage of the QRS complexes and may show small, isoelectric or rarely diphasic or inverted T waves which suggest the presence of myocardial disease.[48] Following treatment with desoxycorticosterone there is usually an increase in the voltage of all the complexes similar to that observed in myxedema following thyroid therapy. Paradoxically, however, treatment with desoxycorticosterone may also be followed by changes denoting progressive myocardial damage.[56]

Occasionally the P-R and Q-T intervals are prolonged. Occasionally also there is a bradycardia at the onset of or during a crisis. These disturbances have been attributed to the action of potassium, the serum concentration of which is increased in advanced stages of Addison's disease. The occasional occurrence of high T waves in Addison's disease has also been attributed to the elevated serum potassium.[55] It is well known that the ingestion of a single large dose of a potassium salt can produce electrocardiographic changes, characterized by a high peaked T wave in all leads, especially the precordial.[55, 33] Flat or inverted T waves in cases of thyroid deficiency may become upright after the ingestion of potassium salts.[50] On the other hand a deficiency of serum potassium, such as occurs in familial periodic paralysis, is associated with low or inverted T waves and depressed S-T interval. Similar electrocardiographic abnormalities occasionally observed during desoxycorticosterone therapy (but with low potassium intake) may actually be due to loss of potassium induced by that steroid.[58]

At postmortem examination the heart is usually described as atrophic.[46] There may be remarkable degenerative alterations of the muscle fibers, but as a rule there are no striking microscopic changes. Goodof and MacBryde[28]

reported interesting findings in the heart of a patient with Addison's disease, who had been treated with desoxycorticosterone and subsequently died of cardiac failure. Throughout all four chambers there were foci of necrosis resembling closely similar lesions in the hearts of rats which had received large amounts of desoxycorticosterone[22] and also resembling those lesions produced in rats which had been maintained on a low potassium diet.[49, 26] The implication is that desoxycorticosterone administered to patients with Addison's disease causes retention of sodium and fluid with simultaneous excretion of potassium; this sudden reduction in serum potassium, especially if the patient is on a low potassium intake, is capable of producing cardiac damage and contributing to the development of congestive heart failure. Thus, myocardial disturbances and corresponding electrocardiographic changes (supra) have been attributed both to the high serum potassium which accompanies Addison's disease and to the reduction in serum potassium which follows effective treatment with desoxycorticosterone and sodium salts.

THE PARATHYROIDS

Pathologic Physiology

The parathyroid glands are concerned with the regulation of calcium and phosphorus metabolism. By increased secretion of their hormone, parathormone, they elevate the level of serum calcium, reduce that of serum phosphorus and enhance the excretion of both calcium and phosphorus, especially the latter. Their physiologic relationship to the heart arises from the fact that calcium (with sodium and potassium) is essential to proper cardiac contraction. The perfused isolated heart will stop in diastole if there is no calcium; an excess of calcium causes systolic arrest (calcium rigor). Like digitalis, calcium increases systolic contraction. Fear of a dangerous potentiating effect is the basis for the purported contraindication to the injection of calcium in digitalized patients (p. 191). In dogs perfused with calcium in such a manner as to cause a progressive increase in serum calcium, Hoff, Smith and Winkler[66] observed bradycardia, T wave changes and finally death from ventricular fibrillation or from cardiac standstill. They concluded that calcium in low concentration was a cardiac stimulant; in high concentration it was a cardiac depressant. Injected parathormone produces effects which are somewhat similar to those of calcium, namely an early increase in heart rate followed by slowing and by cardiac arrhythmia, which is characterized by premature beats and shifting of the pacemaker.[65]

Hyperparathyroidism

Hyperparathyroidism in humans is not associated with distinctive cardiovascular disturbances comparable to those described above as following excessive dosage of calcium or parathormone. However, a shortening of the Q-T interval in the electrocardiogram has been noted,[68, 67] but the degree of shortening was slight and insufficient to be of diagnostic value. A shortening of the Q-T interval also follows digitalis therapy. Hyperparathyroidism is frequently complicated by nephrolithiasis and secondary renal insufficiency. In such cases, hypertension and its cardiovascular complications may develop

(p. 853). Hyperparathyroidism has been mentioned as having a possible role in aging and arteriosclerosis because of the increased content of calcium in the tissues in these conditions.

Hypoparathyroidism

Hypoparathyroidism is usually due to injury or accidental removal of the parathyroids during thyroidectomy. It is characterized chemically by a reduction in the serum calcium and clinically by the occurrence of tetany. Hypocalcemia and tetany may also be caused by an inadequate intake of calcium, e.g., in patients with rickets or osteomalacia, or during pregnancy or lactation, by an inadequate absorption of calcium as a result of celiac disease, sprue or steatorrhea of other etiology, by severe renal insufficiency with phosphate retention, especially when patients with this condition are given alkalis. Other causes of tetany such as hyperventilation and prolonged vomiting may be unaccompanied by hypocalcemia but the percentage of ionized calcium may be reduced.

With respect to the heart, these various conditions associated with hypoparathyroid or other hypocalcemia are of interest because they are documented electrocardiographically by a significant and sometimes striking prolongation of the Q-T interval.[61] As the hypocalcemia is corrected, the Q-T interval is restored to normal. While a prolongation of the Q-T interval is most distinctively associated with conditions in which there is hypocalcemia, the Q-T interval may also be prolonged on occasion in cases of hypoglycemia, diabetic acidosis, alkalosis, beriberi, quinidine toxicity, heart failure and various forms of myocardial disease in which there is pronounced cardiac enlargement, and in some cases of advanced heart block or bundle branch block.

The normal Q-T interval,[63] which represents electrical systole, varies inversely with the heart rate: i. e., the slower the heart rate or the longer the interval between beats (R-R interval) the longer the Q-T interval. The latter is somewhat longer in women than in men. Various formulae have been devised to determine what is a normal Q-T period:

$Q\text{-}T = K\sqrt{R\text{-}R}$ where R-R is the cycle length. This is Bazett's[62] formula, the one most commonly employed. The Q-T interval is considered prolonged if K exceeds 0.39 in men or 0.42 in women. Somewhat different figures have been obtained for K by Bazett,[62] Cheer and Li[64] and by Shipley and Hallaran[69]; the latter noted a higher range of normals than the others. Ashman[60] suggested the following: $Q\text{-}T = K \log [10(R\text{-}R) + .07]$ where R-R = cycle length in seconds and K = 0.385 second for women and K = 0.375 for men and children. At heart rates of 70 or over the upper limit of normal is 0.42 second for women and 0.41 second for men and children. At heart rates of 100 or more the Q-T interval should not exceed 0.35 in women or 0.34 in men and at rates of 45 it should not exceed 0.47 for men or 0.48 for women.

TESTES AND OVARIES

The sex hormones of the testes and ovaries are concerned chiefly with the growth, development and functional activity of the sexual organs, and with the development of secondary sex characteristics. In addition the sex hormones produce certain metabolic effects which resemble those of the adrenal cortex, whose hormones are chemically related. Thus testosterone, the most active of the male hormones (androgens), causes a retention of salt and fluid, probably by its effect on the renal tubules. The occurrence of premenstrual edema was mentioned above as an anterior pituitary effect, but it may be related directly or indirectly to ovarian function. Of recent interest are the

claims that testosterone, by causing vasodilatation, is useful in the treatment of peripheral vascular disease and of angina pectoris.

Tumors of the male or female sex organs are not associated with distinctive physiologic or clinical cardiovascular effects. Masculinizing tumors of the ovaries may be responsible for manifestations of the adrenogenital syndrome but the hypertension and metabolic changes seen in Cushing's syndrome are absent. Diminution in secretion of the ovaries or testes due to disease or atrophy, especially at the menopause, may be associated with vasomotor and functional cardiovascular disturbances such as flushes, sweats, palpitation and tachycardia. Psychic factors are also important in the causation of these symptoms. Hypertension often develops at the time of the menopause; its relation to the sex glands is uncertain. Scherf[70] described electrocardiographic changes, including ST segment depressions in all limb leads and lowering of the T waves, in women with hypoovarian function. These alterations were corrected by estrogen therapy. That these minor electrocardiographic deviations are specifically due to ovarian deficiency is questionable. Former belief in the existence of heart disease secondary to uterine fibromata has almost completely faded.

THYMUS

The thymus has been related in function to the sex glands, the pituitary, thyroid and adrenals. Thymic tumors have been associated with the complete Cushing's syndrome, including the hypertension.[72] Such tumors have been held responsible for myasthenia gravis, cure of which has followed the removal of a thymic tumor. Usually the thymus gland atrophies after puberty; its persistence has been noted in patients with hyperthyroidism and other endocrinopathies. A persistent enlarged thymus and hyperplasia of the lymphoid tissues (status thymicolymphaticus) are sometimes associated with notable hypoplasia of the heart, aorta and other vessels and occasionally with sudden death after minor trauma or infection. The relationship of the enlarged thymus and lymphoid tissue to sudden death is obscure. In fact the whole concept of status thymicolymphaticus has been rejected.[74] Raab[73] has attributed sudden death in young individuals to ventricular fibrillation caused by excessive amounts of epinephrine-like substances in the heart. There was a recent report of sudden death in identical twins who were able athletes.[71] The autopsy in one disclosed hyperplasia of the thymus and hypoplasia of the aorta but there was also pronounced arteriosclerosis. Attention has already been directed to recent evidence that acute coronary thrombosis is a not uncommon cause of death in young individuals (p. 405).

THE PANCREAS

Hyperinsulinism and Hypoglycemia

Excessive secretion of insulin such as occurs in islet-cell tumors of the pancreas, or overdosage with insulin in the treatment of diabetes mellitus or in the shock treatment of schizophrenia, results in hypoglycemia. Hypoglycemia may occur also in cases of adrenal, pituitary or hepatic insufficiency and in some diseases of the diencephalon. Hypoglycemia is of serious concern to patients with angina pectoris or myocardial damage secondary to coronary

arteriosclerosis, for attacks of angina pectoris and of myocardial infarction have been attributed to too vigorous insulin therapy and consequent hypoglycemia.[103, 76]

Aside from the serious neuropsychiatric manifestations of hypoglycemia such as anxiety, confusion, ataxia, syncope, convulsions and coma, there are striking vasomotor and cardiovascular signs such as sweating, pallor, palpitation, tachycardia and a slight rise in blood pressure. Many of these effects resemble those of epinephrine. It may be that they are actually due to a compensatory secretion of the latter, which tends to restore the lowered blood to normal by converting hepatic glycogen into glucose.[81] On the other hand a reduction in blood sugar may directly interfere with cardiac metabolism and produce effects similar to those caused by myocardial anoxia.[77]

In the electrocardiogram, insulin hypoglycemia is documented by a depression of the ST segment, most commonly in leads I, II or both, and by low or diphasic T waves in these leads.[90] These nonspecific changes resemble those caused by epinephrine, but similar changes are observed in patients with angina pectoris during attacks or after an anoxemia or exercise test (p. 379). Similar changes have been described in schizophrenic patients treated with insulin shock. In addition to ST depressions and T wave changes, prolongation of the P-R and Q-T intervals were noted.[83, 82]

Diabetes Mellitus

The fundamental importance of diabetes in cardiology rests on the frequency with which this disease is accompanied by atherosclerosis and its complications, especially coronary artery occlusion.[100, 102] It is a striking fact that the mortality from coronary and peripheral arteriosclerosis among diabetics has increased sharply despite the fact that carbohydrate metabolism has been controlled and the mortality from acidosis greatly reduced.

Advanced coronary atherosclerosis has been encountered in a higher percentage of necropsied cases of diabetes than in those without diabetes.[76, 91, 80, 88] Clinical evidence, i.e., angina pectoris and coronary occlusion, has been observed with much greater frequency among diabetic than among nondiabetic individuals.[94, 78, 93] (See also p. 404.) While coronary occlusion among nondiabetics is very predominantly a disease of males (p. 405), among diabetics women suffer an occlusion as often as men.[102] This strongly suggests the predisposing effect of diabetes. Not only does diabetes appear to enhance the likelihood of developing coronary atherosclerosis, but also it seems to hasten the time of its appearance, for coronary occlusion and other forms of atherosclerosis are encountered among relatively young diabetics.[99, 92, 96]

The frequency of atherosclerosis increases with the duration of the diabetes. Recent studies indicate that almost every diabetic is an actual or potential victim of advanced atherosclerosis of the heart, extremities or retinal vessels.[85, 79]

Hypertension is common among diabetics,[87, 95] but an etiologic relationship is uncertain. In recent years attention has been directed to the syndrome of diabetes, hypertension and severe albuminuria, often with peripheral edema and retinopathy.[86, 98] The pathologic basis of this syndrome is an intercapillary glomerulosclerosis. Hypertension also accompanies diabetes in cases of angina pectoris or coronary occlusion, especially among women. An interesting association of hypertension with diabetes (or diminished glucose toler-

ance) was mentioned as occurring in cases of acromegaly (p. 943) and Cushing's syndrome (p. 945). Russi et al.[97] recently observed that diabetes and hypertension occurred five times as frequently in cases in which necropsy examination revealed small adenomata of the adrenal cortex as in the cases in which an adrenal adenoma was absent. The association of diabetes, hypertension and advanced atherosclerosis in patients with gross disease of the anterior pituitary (acromegaly), adrenal cortex (Cushing's syndrome) and thyroid (myxedema), suggests the fruitfulness of a search in the endocrine organs for a possible common denominator in the etiology of these diseases.

Hypertension and coronary atherosclerosis in diabetics may be terminated by an acute coronary occlusion, sometimes when the latter is the first clinical manifestation. Often myocardial disease and strain secondary to coronary atherosclerosis and hypertension lead eventually to clinical manifestations of congestive heart failure. A relative deficiency of vitamin B_1 in diabetes mellitus should be considered as a possible contributory factor in the development of heart failure.

The common occurrence of acute myocardial infarction in diabetics presents problems in diagnosis and therapy. The acute coronary incident is sometimes associated with hyperglycemia, glycosuria and ketonuria as well as with shock and occasional nausea and vomiting. An erroneous diagnosis of impending coma, based on the laboratory findings, may be considered while the cardiac infarction is overlooked. On the other hand diabetic coma may actually occur with or be precipitated by an acute coronary occlusion. The diabetes is properly diagnosed and treated but the occlusion may not be recognized.

The association of acute coronary occlusion with diabetic coma requires special caution in treatment lest an overenthusiastic administration of insulin enhance the myocardial disturbance already present, or a too vigorous administration of fluids, especially as saline, overload the damaged heart and induce congestive heart failure. Haste in the correction of shock, dehydration and ketosis is essential but continuous clinical observation and chemical study are necessary to avoid a cure of the diabetic acidosis with loss of the patient from cardiac disability. Similarly in the treatment of all cases of longstanding diabetes, especially in elderly patients, it should be assumed that pronounced coronary arteriosclerosis is probably present and sharp reductions in the blood sugar by diminishing carbohydrate intake or increasing the dose of insulin should be avoided.[101] An intake of less than 125 to 150 gm. of carbohydrate daily is rarely advisable. While correction of acidosis is essential and of glycosuria is desirable, a moderate hyperglycemia should be maintained as a reserve against excessive reductions in blood sugar. This denotes minimal insulin dosage.

Diabetic Coma

Certain electrocardiographic abnormalities have been observed in patients during and on emergence from diabetic coma.[75, 84, 89] The chief alterations are a prolongation of the Q-T interval, depression of the ST segment and diphasic or inverted T waves. These findings resemble those associated with hypoglycemia or insulin shock. The ST and T wave alterations resemble those of generalized myocardial anoxia due to coronary insufficiency. The changes may be most pronounced, not during the actual coma, but a day after recovery. The low T waves may be correlated with low serum potassium levels which

occur during recovery from diabetic coma.[82a] Almost always the electrocardiogram later reverts to normal.

HEMOCHROMATOSIS

Hemochromatosis or bronze diabetes is a metabolic disease characterized by pigmentation of the skin and internal organs, diabetes and frequently cirrhosis of the liver. The iron-containing pigment is also deposited in the heart muscle in most cases, but fibrosis is rare.[105, 106] However, occasionally there have been reports of heart failure in cases of hemochromatosis, not explained by the usual forms of heart disease.[107, 104, 110, 107a] In the case of Kerr and Althausen[108] and in the case reported by Petit,[109] complete heart block was present as well as the evidence of heart failure. The nature of the cardiac disturbance and the pathogenesis of the heart failure are obscure, but the latter has been attributed to extensive deposition of hemosiderin and myocardial degeneration. The occurrence of cardiac pain in some cases has led to a mistaken diagnosis of acute coronary occlusion.

NUTRITIONAL DISTURBANCES

Obesity

While obesity is ultimately the result of an excessive caloric intake relative to the metabolic requirements of the body, there is considerable evidence that disturbances in the diencephalon and psychic factors may be important in its pathogenesis. The relation of endocrine disturbances to obesity is noted in cases of adrenal cortical or anterior pituitary tumors causing Cushing's syndrome and in cases of myxedema.

With respect to the cardiovascular system, obesity has several important relationships. There have been many studies which indicate a correlation between obesity and hypertension, especially systolic hypertension.[125, 115, 120] Weight reduction often effects a fall in the blood pressure of obese hypertensive individuals.[121] There is also some evidence that coronary arteriosclerosis and occlusion are more common in the obese (p. 406).

Obesity influences the roentgen ray appearance of the cardiac silhouette and the electrocardiographic tracing. By causing elevation of the diaphragm the heart assumes a transverse position and the left ventricle may appear enlarged in the anteroposterior view. The presence of a large apical fat pad may enhance this effect by obscuring the apex. Views in deep inspiration minimize these distortions. In the electrocardiogram, the limb leads frequently disclose an inversion of T_3 and left axis deviation.[122]

Fatty infiltration of the surface of the heart is common in obese subjects. The epicardial fat is increased and encases most of the heart, especially the right ventricle and the interventricular sulcus. It may even penetrate the superficial muscle bundles.[126] But fatty *infiltration* is not a form of heart disease and is not responsible for clinical symptoms. Fatty *degeneration* of myocardial fibers results most often from anemia and infections, and occasionally from phosphorus or other poisoning.

Moderate dyspnea on exertion is common in obese persons partly because of the abnormal strain of the ballast on the circulation,[123] and partly because obese individuals do not exercise and lack training. Dyspnea in the very obese or dyspnea which develops concomitantly with pronounced weight gain should

be carefully evaluated to avoid misinterpreting it as a symptom of congestive heart failure. Excessive weight may also exaggerate symptoms in patients with heart failure due to independent organic heart disease. In such cases weight reduction is an important part of the therapeutic program.

Undernutrition and Starvation[116]

Undernutrition leads to a reduction in cardiac weight which is proportional to or slightly less than the reduction in total body weight.[117] This is accompanied primarily by atrophy of myocardial fibers, but with prolonged and severe starvation brown atrophy, fatty and other degenerative changes appear.

The basal metabolism is depressed and the cardiac output (minute volume) as well as the stroke output is diminished. The cardiac work is reduced; because of this, undernutrition has been employed in the treatment of hypertension, acute coronary occlusion and heart failure.

There is pronounced sinus bradycardia. The circulation time is prolonged, the venous pressure depressed and the blood pressure and pulse pressure diminished, the systolic falling more than the diastolic. The extremities tend to be cold, pale and slightly cyanotic.

There are few *symptoms* referable to the circulatory system. Dizziness may occur with sudden rising. Syncope may result from prolonged standing. Dyspnea, palpitation and precordial pain are absent. Edema is often a prominent feature, but is not attributed to heart failure, as the heart is not enlarged and the venous pressure is low or normal. The circulating blood volume and extracellular fluid are increased.[111]

The electrocardiogram shows, in addition to bradycardia, a reduction in the voltage of all deflections, a prolonged Q-T interval (but not necessarily prolonged in relation to the cardiac cycle), right axis deviation, and only occasionally depression of the RST segment, alteration of T waves and a prolongation of the P-R or QRS intervals.[112, 113, 124]

The exact mechanism for starvation edema is uncertain. The classic belief that it is due to pronounced hypoproteinemia, especially to the reduction in plasma albumin, has recently been supported by the findings in German civilian internees[111] and in the civilian population of Saipan during the war.[119] However, this viewpoint has been challenged[114, 118] because of the occasional appearance of famine edema when the plasma proteins were normal, because of the absence of edema in some instances of hypoproteinemia, and occasional clinical improvement with profuse diuresis and loss of edema before there is a significant change in the concentration of plasma protein. These imperfect correlations between hypoproteinemia and edema probably do not invalidate the belief that the latter is due chiefly to the reduction in colloid osmotic pressure associated with diminution in plasma protein, according to the Starling theory. However, other factors, such as variations in tissue pressure, presence of dehydration, and especially the degree of inactivity or activity, may account for discrepancies. Famine edema sometimes diminishes or disappears with bed rest and increases with physical exertion. Exercise may increase the venous return beyond the capacity of the atrophic heart to accept; edema may appear or increase because of a consequent elevation of venous pressure or a diminution in renal blood flow with secondary retention of sodium and water.

Although manifestations of congestive heart failure are usually absent even

with prolonged starvation, they may appear rapidly if nutritional rehabilitation is effected too enthusiastically,[110a] or if fluid balance is restored too rapidly. Dyspnea, tachycardia and cardiac enlargement may develop and there may be a recurrence of edema associated with an elevated venous pressure.

Vitamin Deficiency

Vitamin B_1 Deficiency—Beriberi Heart. Cardiovascular manifestations are often associated with the so-called wet form of beriberi. These cardiac disturbances were described in cases of beriberi in the Orient by Shimazono[152] and by Aalsmeer and Wenckebach,[127] in cases in this country by Scott and Herrmann[150] and by Weiss and Wilkins[154] among others, and recently in cases in Cuban children by Junco[139] and by Abrilli.[128] Weiss and Wilkins[154] were able to report in 1937 on 120 cases of beriberi with cardiovascular as well as neurologic manifestations in the Boston City Hospital, an incidence far greater than the occasional case encountered in most hospitals. While beriberi in the Orient and elsewhere is due usually to a diet limited to polished rice, in this country it has often been observed in alcoholics or drug addicts. A restriction in food intake, neurotic adherence to food fads, poverty with consequent caloric and vitamin deficiency, and occasionally diabetes, pregnancy and severe gastrointestinal disease have been causative or contributory factors. Pellagra is often, and scurvy occasionally, combined with beriberi in the same patient.

Symptoms. The cardiac symptoms often start with palpitation, fatigue and rapid heart beat. Breathlessness and peripheral edema develop early. Progressive dyspnea, orthopnea, attacks of cardiac asthma or pulmonary edema appear as evidences of left-sided heart failure. Increasing subcutaneous edema, serous effusions, engorgement of the cervical veins and enlargement of the liver result from failure of the right side of the heart. Aalsmeer and Wenckebach[127] described only symptoms of right-sided heart failure in their cases of Oriental beriberi. Shock may result from acute cardiac failure or from acute peripheral vasodilatation. Late in the disease syncope with fall in blood pressure and other symptoms of shock dominate the clinical picture.

Objective Findings. Physical examination discloses, besides the neurologic signs, enlargement of the heart in severe cases, muffled first heart sound, systolic murmurs, embryocardia and gallop rhythm. In the Cuban cases, murmurs, arrhythmias and cardiac enlargement were not observed.[139] The superficial veins are engorged and the venous pressure elevated. The pulse may be bounding and pistol-shot sounds may be heard over the femoral arteries. Corresponding to these vascular signs there is a pronounced increase in the pulse pressure, but the mean arterial pressure is normal. The pulse rate is rapid. The skin is usually warm. However, these peripheral vascular phenomena may be absent and the clinical findings may be indistinguishable from those of heart failure due to other types of heart disease.

The Electrocardiogram. The electrocardiogram may disclose depressed diphasic or inverted T waves. Low voltage of the QRS complexes and a prolongation of the Q-T interval occur not infrequently.[133] Tachycardia is usual. With successful treatment there is observed slowing of the heart rate, increased voltage and disappearance of T wave abnormalities.

Roentgenologic examination often reveals cardiac enlargement which re-

gresses on a regime of bed rest and large doses of thiamine chloride.[132, 134] Garland and McKenney[137] noted an enlarged, poorly contracting heart with mild pulmonary congestion in cases of beriberi heart disease.

Morphologic Changes. Postmortem examination reveals occasional cardiac hypertrophy, but frequently the hearts are of normal weight.[154] Aalsmeer and Wenckebach[127] stressed the occurrence of right ventricular dilatation. Histologic examination usually discloses a normal myocardium but there may be hydropic degeneration of the myocardial fibers, separation of the myocardial bundles, swelling of the collagen and perivascular and interstitial "edema."[153] The cardiac manifestations of beriberi may be attributed to actual anatomic abnormalities in some cases[155] but the lesions described are nonspecific and often absent. It is more likely that disturbances in carbohydrate metabolism, incident to thiamine deficiency, produce derangements in cardiac function which may or may not have a visible anatomic basis. Recent observations showed that the hearts of thiamine-deficient dogs were unable to absorb pyruvate from the blood as do normal hearts.[147] In fact in these animals the T wave changes observed in the electrocardiogram could be correlated with an outpouring of pyruvate from the heart.

Pathologic Physiology. Many of the cardiovascular manifestations of beriberi probably originate in the peripheral vascular system and resemble those encountered in anemia, hyperthyroidism, fever or arteriovenous fistula. Peripheral vasodilatation, i.e., diminished peripheral vascular resistance, results most probably from acidic metabolites (pyruvic and lactic acid). These accumulate because of the lack of thiamine which is essential for cocarboxylase, the enzyme required to oxidize pyruvic acid.

The diminished peripheral resistance has the effect of multiple arteriovenous shunts which greatly accelerate the speed of the circulation. However, Keefer[140] noted accelerated circulation in only one third of the cases he observed in China and Blankenhorn et al.[132] stressed that acceleration of the circulation is rare in Occidental beriberi as observed in this country. In the presence of heart failure the circulatory acceleration due to uncomplicated beriberi may be obscured, or because of mental dulness it may be difficult to perform a reliable test of circulation time. When the speed of the circulation is accelerated, the venous return and the minute cardiac output are increased. Nevertheless heart failure occurs despite the abnormally great cardiac output, because although elevated the output is still relatively inadequate to supply the tissues whose oxidative metabolism is impaired. The venous pressure becomes elevated. Oxygen consumption is increased and the arteriovenous difference is small.[144] Heart failure in beriberi may be considered to result from: (1) the thiamine-deficient metabolism of heart muscle,[137a] (2) increased work of the heart due to augmented venous return and cardiac output. It is probable that there is a stage of beriberi in which the circulation is accelerated and the venous return and minute volume increased without congestive heart failure, just as there are prefailure stages of increased circulation in arteriovenous fistula and hyperthyroidism.

Diagnosis. The diagnosis of beriberi heart is based on the recognition of the cardiovascular abnormalities in association with other evidences of beriberi such as tenderness and swelling of the calves and peripheral neuritis. There may also be concomitant signs of pellagra and occasionally of scurvy such as psychosis, dermatitis, glossitis, diarrhea, anemia, dysphagia and purpura.

Beriberi heart must be considered as the etiologic type in all cases of unexplained cardiac enlargement or unexplained cardiac failure. A normal or diminished circulation time in the presence of heart failure suggests beriberi heart if hyperthyroidism can be excluded and fever is absent. Severe anemia of various etiologies may produce somewhat similar circulatory disturbances but should not lead to confusion with beriberi heart. In the American cases of beriberi heart disease rapid circulation is often absent or insignificant or it may be overshadowed by the slowing due to congestive heart failure. The response to the administration of thiamine chloride is of diagnostic importance, but failure to improve does not exclude the diagnosis of beriberi heart disease. Above all a careful dietary history may aid in supporting or rejecting the diagnosis of beriberi heart. On the basis of 10 cases studied at the Cincinnati General Hospital, Blankenhorn[131] emphasized the following diagnostic criteria: (1) enlarged heart with normal rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis or pellagra, (5) gross deficiency of diet for three months or more, (6) no other cause for the heart disease, (7) clinical improvement and reduction of heart size after specific treatment. In recent years there has been a tendency to liberalize the diagnostic criteria of beriberi heart disease and to consider this diagnosis in all cases of heart failure of obscure origin in which there is a history of dietary deficiency in thiamine chloride.[129]

Treatment. Thiamine chloride, given subcutaneously in doses of 100 mg. daily, is the specific treatment. An adequate protein intake is important for the proper utilization of thiamine. In most instances in which the disease is not of long duration nor far advanced, the response is extremely favorable and rapid. Signs of congestive heart failure, including anasarca, disappear first; later the enlarged heart returns to normal size[137] and the electrocardiographic abnormalities disappear. On the other hand, too zealous a caloric intake may at first induce an exacerbation of symptoms. Occasionally in cases of chronic thiamine deficiency the myocardial changes are irreversible or only partially reversible. The clinical response may be slow or unsatisfactory. Relapses after apparent recovery are not uncommon.

Rest in bed is an important adjuvant in therapy. Anasarca may disappear after rest in bed alone. Conversely, as in cases of edema due to undernutrition, exercise intensifies the manifestations of the disease or may precipitate a recurrence following recovery. Sodium salts should be restricted. Mercurial diuretics and digitalis should be given as in other cases of congestive heart failure. But their effectiveness will be only slight or moderate so long as the vitamin deficiency is uncorrected. Other vitamin deficiencies should also be corrected by the administration of niacin, ascorbic acid, vitamin K, etc., and a high caloric diet rich in protein should be given. Correction of the anemia may require iron, liver and/or folic acid. Since infection may precipitate cardiac symptoms when there is an underlying vitamin B deficiency,[149] this factor should be sought and eliminated.

Pellagra. Pellagra is often combined with beriberi. It is probable that the cardiovascular disturbances formerly attributed to pellagra are due entirely or chiefly to beriberi. However, electrocardiographic abnormalities have been correlated specifically with pellagra or niacin deficiency.[141] Feil[136] noted electrocardiographic alterations in 40 per cent of 38 cases of pellagra. Most commonly there was an inversion of T_1 or T_2 or both (16 per cent), coronary

T wave (13 per cent), inversion or eversion of ST, large T in at least one lead and low voltage (18 per cent). Q-T was slightly lengthened in some cases. There were no roentgenologic abnormalities and no pathologic lesions were discovered at postmortem examination.

Similarly Porter and Higginbotham[145] observed electrocardiographic abnormalities in 10 of 25 cases of pellagra, but they interpreted the changes as nonspecific and due to vascular or toxic complications. More recently Rachmilewitz and Braun[146] described 16 cases of pellagra in which electrocardiograms disclosed T wave inversions which reverted to normal after niacin



Fig. 78. Von Gierke's disease in an adult. Generalized cardiac enlargement.

therapy but not after thiamine administration. Despite these interesting reports it is uncertain whether significant cardiac dysfunction may result specifically from pellagra.

Other Vitamin Deficiencies. Cardiac disease has been attributed to a lack of vitamin C (ascorbic acid) on the basis of experimental studies. Deficiency of ascorbic acid has been especially related to the development of rheumatic fever and rheumatic heart disease.[148, 143, 151] There has been no acceptable support for these relationships in humans. Hemorrhagic pericardial effusions have been reported in severe cases of scurvy[138] as part of the hemorrhagic tendency. Erdheim[135] described the occurrence of cardiac hypertrophy in children dying of scurvy and referred to the enlarged heart as "Barlow-Herz." In the absence of adequate clinical data, the possibility that he was dealing with associated beriberi heart disease cannot be excluded.

Cardiac disease due to vitamin D deficiency was reported by Meixner.[142] Here too it is probable that the changes described were due to associated thiamine deficiency.

On the other hand, excessive vitamin D ingestion has resulted in metastatic calcification with gross and microscopic calcific deposits in arterial media, myocardium and cardiac valves.[130]

VON GIERKE'S DISEASE—GLYCOGEN CARDIOMEGALY

This is a metabolic disease characterized by an abnormal storage of glycogen in the liver and other organs.[158] Of interest to the cardiologist are the cases in which excessive glycogen storage in the heart leads to an increase in the size and weight of that organ.[156, 159] Clinically these cases present the problem of cardiac enlargement without apparent cause. Pathologically they have been mistakenly incorporated in the motley group of cases of idiopathic hypertrophy of the heart. Rhabdomyomata of the heart have been interpreted as glycogen-rich muscle fiber accumulations representing a local form of von Gierke's disease (p. 997).

Clinically the cardiac form of von Gierke's disease may appear as cardiac enlargement (Fig. 78) of undetermined etiology, but its nature may be suspected if there are also signs of hepatic involvement. In the latter circumstance there may be also hepatomegaly, ketonuria (especially in the morning), fasting hypoglycemia, elevated blood cholesterol and blood glycogen and abnormal blood sugar responses to epinephrine, levulose, etc. Sudden death has been reported in cases of glycogen disease with cardiomegaly.[157]

XANTHOMATOSIS

This is an hereditary disorder of lipid metabolism characterized by (1) yellowish plaques and nodules (xanthoma) over the elbows, knees, buttocks, and over the tendons and joints of the fingers, toes, wrists and ankles, and also xanthelasma of the eyelids; (2) hypercholesterolemia; and possibly (3) xanthomatous biliary cirrhosis.[165]

This type of primary xanthomatosis (xanthomatosis tuberosa), which is associated with an elevated serum cholesterol, is of great cardiologic interest because of the frequency of angina pectoris, coronary occlusion and sudden death in families subject to this metabolic disorder.[163, 164] Intermittent claudication, due to involvement of the vessels of the extremities, may also occur. However, hypertension is unusual.

A characteristic feature is the early age at which these serious complications often appear.[162] Thus Bloom, Kaufman and Stevens[160] reported that of 5 children of a single family affected by this disease 4 died suddenly between the ages of six and twenty-three years, the cause of death being attributable to xanthomatous lesions in the cardiovascular system. Necropsy observations in one of the fatal cases, in which death occurred at twenty-three years of age, showed advanced atheromatosis of the aorta and coronary arteries and myocardial degeneration of the heart. Typical foam cells were seen in the microscopic lesions of the aorta.

The hypercholesterolemia is of interest because of the possible relationship to the development of atherosclerosis (p. 339). Hypercholesterolemia without cutaneous lesions may be found in some members of families with xanthomatosis.[161] This suggests that the elevated serum cholesterol is the fundamental

manifestation of the metabolic disorder.[166] According to Wilkinson et al.,[166] the disease is inherited as an incomplete dominant, xanthoma tuberosum representing the homozygous and hypercholesterolemia with xanthelasma the heterozygous abnormal. The increase in blood cholesterol is endogenous, not dietary, and is influenced little if at all by restriction of cholesterol intake.

The *diagnosis* of familial xanthomatosis of the cardiovascular system should be considered whenever angina pectoris or coronary occlusion occurs among young adults or whenever there are characteristic xanthomatous cutaneous nodules and plaques associated with hypercholesterolemia. A careful history may add confirmation by disclosing the occurrence of sudden death in siblings and parents at very early ages. Members of the afflicted patient's family should have determinations of the blood cholesterol even if there are no symptoms and cutaneous lesions. Exclusion of eggs, animal fats and other cholesterol-containing foods and the administration of thyroid are therapeutic recommendations of undetermined value.

AMYLOIDOSIS OF THE HEART

Amyloidosis is a disease of uncertain pathogenesis, in which a peculiar protein substance is deposited in the reticuloendothelial system and the pericapillary and collagenous tissues of various organs.[175] Amyloidosis may be classified into (1) secondary and (2) primary systemic forms. The secondary form is found in association with chronic pulmonary tuberculosis, chronic pulmonary, bony or other suppuration, syphilis, multiple myeloma, neoplasm, Hodgkin's disease or leukemia. The amyloidosis is usually generalized, the spleen, liver, kidney, suprarenals and lymph nodes being most often affected. Only occasionally is the heart involved.

The *primary form*[170] is said to differ in the absence of a specific etiologic disease and absence of amyloid or only minimal deposition in the liver, spleen or kidney, while amyloid is common in the heart, skin, lungs, muscles and other sites not involved in the secondary form. However I have seen primary amyloidosis with the typical distribution in spleen, liver and kidney and involvement of the heart.

While the exact pathogenesis of amyloidosis is unknown, it has been experimentally produced by repeated injection of sodium caseinate and foreign proteins, serum protein, egg albumin and by repeated injection of toxin into horses for production of antisera. In some human cases which I have observed prolonged undernutrition with limitation of protein intake to milk and milk products may have been significant. Amyloidosis appears to be reversible in cases in which a suppurative focus is removed.

The cardiologist is particularly interested in the primary systemic (atypical) form of amyloidosis in which there is almost always extensive cardiac involvement. About 50 cases of primary or atypical amyloidosis have been studied and reviewed.[171, 169, 174, 176, 173] In about half, heart failure developed.[166a] Dyspnea, orthopnea, attacks of cardiac asthma, cough, weakness, palpitation and precordial pain are the commonest symptoms. Examination during the stage of heart failure may reveal cardiac enlargement, tic-tac sounds (embryocardia), cardiac murmurs, gallop rhythm and pulsus alternans. In the presence of right-sided failure there may also be subcutaneous edema, hydrothorax and ascites. The *electrocardiogram* may disclose low voltage of the QRS complex.

Pathologically, the amyloid forms grayish nodules or diffuse thickening which cause a leathery rigidity and enlargement of the walls of the ventricles and atria.[167] Frequently the amyloid affects the valves and may produce nodules and rigid thickening which interfere with valvular function.[172, 171, 178] The coronary arteries as well as smaller vessels may be affected; occasionally amyloid infiltration contributes to the coronary narrowing.

Congestive heart failure is due chiefly and most commonly to extensive myocardial involvement by amyloid, which compresses and damages the muscle fibers and interferes with contraction and relaxation. However, coronary artery involvement with narrowing of these vessels, valvular infiltration with consequent insufficiency and stenosis, or extreme infiltration and narrowing of the small pulmonary arteries with secondary chronic cor pulmonale[177] are among occasional causes of congestive heart failure in primary amyloidosis.

The *diagnosis* of amyloid disease of the heart is to be considered in the presence of cardiac enlargement or heart failure without apparent cause. A supporting clue may be found in associated amyloid deposits proven by biopsy, e.g., in the skin simulating scleroderma, in the tongue causing macroglossia or tumor formation, in the muscle simulating myotonia or occasionally in the tissues about the joints, larynx and other sites. A congo red test may be helpful but this may be negative in the primary type of amyloidosis, in which the liver is not involved.

Treatment of primary amyloidosis involving the heart is unsatisfactory. The use of liver powder (4 to 8 gm. daily) has been suggested.[168] In the presence of congestive heart failure, the usual therapeutic measures should be employed (p. 160).

ACUTE PORPHYRIA

This disease is characterized by psychic instability, abdominal pain and findings resembling ileus, flaccid paralyses and porphyrin in the urine, with or without photosensitivity. Hypertension and renal disease are frequently associated, possibly due to the arteriospasm of the general disease. Eliaser and Kondo[179] reported elevations of the RT segment in lead I, diminished voltage of the QRS and left axis deviation. These changes disappeared during the period of remission. The authors suggested that the electrocardiographic changes were due to transient angiospasm in acute porphyria which involved the coronary arteries as well as other blood vessels.

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THE HEART AND CIRCULATION IN ANEMIA

Anemia may affect the heart by direct impairment of its oxygen supply or by increasing its mechanical load through the alteration of its circulatory dynamics. When severe anemia develops acutely from rapid and profuse blood loss, symptoms of shock may dominate the picture, not because of anemia but because of an insufficient cardiac output due to a deficient blood volume.

Anemia and Preexisting Heart Disease. Intense chronic anemia produces anatomic and physiologic disturbances, as a rule, only when the heart is already diseased, but occasional instances of failure of a normal heart purportedly due to anemia alone have been reported.[5, 54] Anemia is particularly apt to cause serious anoxia in the myocardium which is already predisposed by severe coronary arteriosclerosis, or in the enlarged rheumatic heart with its exaggerated need for oxygen.

I have repeatedly observed in patients with arteriosclerotic or rheumatic heart disease the precipitation of heart failure and coronary insufficiency by severe anemia due to a bleeding peptic ulcer or occasionally due to a bleeding colonic or gastric neoplasm, bleeding hemorrhoids or ulcerative colitis.[10, 34] In such cases elevation of the level of hemoglobin is often the only effective method of eliminating the cardiac and circulatory symptoms. Care should be employed not to precipitate acute pulmonary edema by too rapid or too large transfusions of blood.[49] The use of concentrated red blood cells with minimal plasma is preferable to that of whole blood if the deficiency is due entirely to the anemia and not to inadequate blood volume. The patient should be propped up in bed during the transfusion to reduce the possibility of inducing pulmonary edema. Repeated determinations of vital capacity and venous pressure may disclose impending or actual overhydration of the lungs or subcutaneous tissues before they are discovered by physical examination.[20]

Degree of Anemia. Contrast between Chronic Anemia and Acute Hemorrhage. As a rule cardiac manifestations and circulatory disturbances appear in chronic anemias only when the anemia is very severe. According to Brannon, Merrill and associates,[11] serious disturbances did not usually occur in their patients until the hemoglobin fell below 7 gm. per 100 cc., but moderate circulatory abnormalities appeared when the hemoglobin level was between 9 and 8 gm. The circulatory abnormalities result exclusively from the deficient oxygen content of the blood and are recounted below.

In acute hemorrhage the problem is quite different and relates to the reduction in circulating blood volume and the physiologic compensations to that reduction. Loss of about 500 cc. of blood results in slight tachycardia, a slight fall in atrial pressure and little or no reduction in cardiac output.[41, 55] Occasionally a fall in blood pressure and collapse result from reflex vasodilatation and a consequent drop in peripheral resistance. But with more profuse rapid blood loss (1000 cc. or more), the blood volume falls, the cardiac output is sharply diminished and the arterial blood pressure drops.[12] The clinical picture of shock develops concomitantly with intense sympathetic vasoconstriction. Later, as hemodilution occurs, the physiologic disturbances are complicated by those due to the anemia itself (infra).

Etiologic Types of Chronic Anemia and Circulatory Disturbance. The cardiac and circulatory disturbances are essentially identical whatever the cause of the anemia, so long as it is severe. As a rule these disturbances occur in chronic anemias for which there is no satisfactory treatment and in anemias with uncontrollable recurrent hemolytic crises. But they may also develop in curable anemias which remain untreated because of lack of facilities or ignorance on the part of the patient.

In former years the anemia known as chlorosis commonly produced cardiac manifestations,[4, 24] but this anemia, possibly nutritional in origin, has mysteriously disappeared or has been absorbed under other classifications. Pernicious anemia was long the common type of anemia associated with cardiovascular disturbances.[46, 17, 27] The discovery and widespread use of liver therapy has minimized the frequency of prolonged anemia of this kind. At present sickle cell anemia is a frequent cause of cardiac and circulatory abnormalities because of the intensity of the anemia (the red blood counts are usually between 2,000,000 and 3,000,000 or less) and because of its relative chronicity and unsatisfactory response to treatment.[57] Of interest also are the cases of intense chronic anemia with cardiac disturbances due to hookworm anemia, studied and reported by Porter.[45] Gelfand[25] called attention to the frequency of very severe anemias and consequent cardiac disability in tropical areas where medical attention is long delayed. Among 42 cases of "heart disease" treated in a native hospital there were 7 with congestive heart failure due to anemia. The hemoglobins in these patients had fallen to between 10 and 20 per cent before hospitalization.

PATHOLOGIC PHYSIOLOGY

A sharp reduction in the hemoglobin and therefore in the oxygen transport power of the blood tends to produce relative tissue anoxia. This deficiency is compensated by a variety of physiologic adjustments which restore an adequate oxygen supply to the tissues. Remarkable as these compensations are, they draw upon the circulatory reserves even when the patient is at rest. In consequence, despite severe anemia, an adequate circulation becomes available when the patient is at rest, but little or no further reserve is available to meet the demands of physical exertion or other circulatory strains. Under the latter circumstances neither the heart nor other tissues may receive an adequate supply of oxygen and the patient may suffer from dyspnea, weakness, angina pectoris or swelling of the legs. But as a rule the following circulatory compensations maintain the patient free of symptoms during ordinary activities despite severe anemia.

Circulation Speed. This is accelerated in cases of severe anemia as demonstrated by Blumgart et al.[9] by means of radium C. I have frequently found the circulation time (calcium gluconate) in patients with hemoglobins between 6 and 8 gm. to vary between 9 and 10 seconds when the normal circulation time varied between 12 and 13 seconds. In general, the velocity of blood flow increases in proportion to the degree of anemia.[50, 54] The circulation speed is not noticeably affected until the hemoglobin falls below 9 gm. or the red blood count below 3,000,000 per cc.; pronounced acceleration occurs only after the hemoglobin level is less than 7 gm.[22] Because of the increased velocity of the circulation, the quantity of blood passing through the tissues in a given time may be increased 100 per cent or more. This permits the tissues to abstract as much oxygen in a unit of time as they would if the hemoglobin content were normal. The findings with the venous occlusion plethysmographic method provide quantitative measurements of the increased blood flow through peripheral tissues.[1]

The *mechanism* by which the circulation speed is increased is probably a peripheral one. The tissue anoxia which develops with the onset of severe anemia leads to the accumulation of acid metabolites which by direct local or reflex action cause peripheral vasodilatation. This concept is supported by the finding of greatly diminished peripheral resistance in severe chronic anemia.[50, 11, 49] Such vasodilatation permits a more rapid venous return to the heart, as if there were multiple peripheral arteriovenous shunts. Analogous mechanisms account for the rapid circulation rate of arteriovenous fistula, hyperthyroidism, beriberi and pregnancy. In addition to this effect, the factor of diminished viscosity due to the low red blood count contributes significantly to the acceleration of circulation.

In cases of intense chronic anemia complicated by congestive heart failure the circulation speed may be normal. The slowing effect of heart failure neutralizes the acceleration due to anemia; the exact resultant depends on the degree of each. In the presence of congestive heart failure, the finding of a normal circulation time should suggest the possibility of an associated severe anemia as well as other conditions which increase the velocity of blood flow.

Oxygen Utilization. Compensation for deficient oxygen content of the blood due to severe anemia may be effected not only by an increased speed of circulation, but also, theoretically, by a more complete abstraction of oxygen from the blood by the tissues. Actually the absolute oxygen utilization per unit of blood is diminished, i. e., the arteriovenous oxygen difference is less than normal.[11, 49] But relative to the amount of hemoglobin oxygen available, the percentage of oxygen utilization is enhanced. Normally the arterial oxygen content reaching the tissues is 19 volumes per cent and the venous oxygen content leaving the tissues is about 14 volumes per cent. Therefore 5 volumes per cent of oxygen have been abstracted or 5/19 (26 per cent) of the arterial oxygen. In a patient with 6 gm. per 100 cc. of hemoglobin the arterial oxygen content is about 8 volumes per cent, while the venous oxygen content may be 5 volumes per cent. The absolute arteriovenous oxygen difference is 3 volumes per cent, which is less than normal, but the percentage of available oxygen utilized is $\frac{3}{8}$ (37.5 per cent), which is more than normal. The reduction in arteriovenous oxygen difference (i. e., the absolute quantity of oxygen abstracted from a unit of blood) is apparently due to the speed with which the blood rushes past the tissues.

Cardiac Output (Minute Volume). That the cardiac output is greatly augmented in cases of severe anemia was demonstrated in animals by Blalock and Harrison[6] and in humans by Plesch,[44] Liljestrand and Stenström,[37] Richards and Strauss[47] and Stewart et al.,[50] among others. Similar findings were more recently noted by the direct Fick method, catheterization of the heart being employed to obtain mixed venous blood.[49, 11] Brannon, Merrill and associates[11] found the cardiac index to be 6.5 (liters per sq. meter body surface area) when the hemoglobin level averaged below 5 gm., 4.7 when the hemoglobin ranged between 5 and 7 gm., 4.0 when the hemoglobin was between 7 and 9 gm. and 3.1 or about normal when it ranged between 9 and 13 gm.

The increased cardiac output results essentially or exclusively from the accelerated speed of the circulation and the consequently augmented venous return. To a variable extent the increase in minute volume is mediated by an *increase in the cardiac rate* but the stroke output is also substantially elevated. Following transfusions and consequent increase in the hemoglobin level, the circulation speed diminishes and the cardiac output falls. When severe chronic anemia is complicated by congestive heart failure, the cardiac output may nevertheless substantially exceed the normal (high output failure). Presumably, although the cardiac output is above normal, it is deficient relative to the needs of the tissues.

The *work of the heart* may not be increased despite the augmented cardiac output, according to the studies of Stewart, Crane and Deitrick[50] in 5 cases of pernicious anemia. Due to peripheral vasodilatation, the peripheral resistance is greatly diminished and the blood pressure is moderately lowered.[29, 54] The work of the heart is proportional to the cardiac output and the mean arterial pressure; the reduction in blood pressure with severe anemia may largely neutralize the effect of the increased cardiac output. The fall in viscosity likewise diminishes the work of the heart. But despite these neutralizing effects it is probable that the work of the heart is increased in cases of very severe chronic anemia and that in such cases increased work is a factor in the production of cardiac strain.

The Circulating Blood Volume. The blood volume in anemia is slightly diminished, chiefly due to the reduction in the number of erythrocytes (low hematocrit[26]). The plasma volume may be normal but often it is slightly elevated.[22] Since the total blood volume is diminished or normal, it is apparent that the augmented venous return and cardiac output in severe anemia result exclusively from the increased speed of circulation. In cases of severe anemia complicated by congestive heart failure the plasma volume may be greatly increased, even to the point of causing an increase in total blood volume.[20] This increase may be viewed as a compensatory mechanism utilized to maintain the cardiac output at required levels.

The *blood pressure* tends to depression of both the systolic and diastolic levels, but especially of the latter. The pulse pressure tends to increase.[29, 54]

The *venous pressure* is not elevated when the patient is at rest, in the absence of congestive heart failure.

The *vital capacity* of the lungs is diminished. The respiratory minute volume and residual air are increased.[8] The explanation for this is uncertain. An increased blood flow through the lungs has been held responsible, but this explanation is unclear.

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Severe longstanding anemia is associated with cardiac dilatation and hypertrophy (see below). In cases of anemia due to acute hemorrhage the musculature is usually firm; in cases of chronic anemia the musculature is flaccid.

Fatty degeneration of the heart muscle is characteristic of intense chronic anemia. It is distributed in a striking fashion, perpendicular to the fibers of the trabeculae and papillary muscles, producing the yellow streaking known as tigering of the heart. The fatty change is presumed to result from disturbances in cellular metabolism due to oxygen deficiency. While fatty degeneration of the myocardium is characteristic of severe anemia, it may also be caused by a variety of infectious processes and toxic substances, as well as extensive severe coronary artery disease.

Of special interest are the changes in the heart observed in instances of intense anemia due to gastrointestinal bleeding in young individuals. In such cases I have observed diffuse focal or confluent areas of myocardial necrosis, chiefly in the subendocardial myocardium of the left ventricle and especially of the papillary muscles.[21] The coronary arteries may be normal. The subendocardial regions have the poorest blood supply and suffer most from anoxia when there is a reduction in blood flow or in the oxygen content of the blood. Similar subendocardial necroses have been produced experimentally in rabbits by bleeding.[13]

CLINICAL FEATURES RELATED TO THE CIRCULATION IN ANEMIA

Severe anemia and the compensatory mechanisms which it invokes are responsible for a variety of clinical manifestations referable to the cardiovascular system. These may closely simulate the symptoms and signs usually due to organic heart disease. It is not uncommon for heart disease and heart failure to be diagnosed because of such manifestations due entirely to anemia alone. On the other hand, severe anemia may precipitate or intensify heart failure or coronary insufficiency in the presence of preexisting cardiac or coronary disease. For this reason it is often necessary to correct the anemia by transfusion or specific therapy in order to evaluate the extent to which anemia is partly or entirely responsible for the symptoms. In this connection it is well to recall that anemias of nutritional origin may be associated also with vitamin B deficiency and that the latter may also contribute to the development of cardiovascular symptoms (p. 955).

Cardiac Enlargement. The outstanding cardiac manifestation of severe chronic anemia is enlargement of the heart. This was demonstrated experimentally in dogs rendered anemic by bleeding.[38] Cabot and Richardson[15] reported significant cardiac hypertrophy in 18 of 19 hearts of patients who had died of pernicious anemia. In one case the heart weight was 710 gm. The possibility of concomitant cardiovascular disease contributing to the development of the hypertrophy may be properly considered in such cases since insufficient data are presented to evaluate the care with which the coronary arteries were studied at that time (1908 to 1919).

The most impressive evidence of cardiac enlargement in severe anemia is presented by roentgenologic observations (Fig. 79*A*). Ball[3] demonstrated by serial films that the cardiac enlargement associated with anemia disappeared following relief of the anemia (Fig. 79*B*). Porter[45] observed cardiac enlarge-

ment regularly in his cases of severe anemia due to hookworm infestation. In most of these the enlargement was reversible, as demonstrated by a reduction in the size of the cardiac silhouette following therapy. But in longstanding cases the size of the heart remained unaltered, an observation which led Porter to conclude that the enlargement in these cases was due to hypertrophy. Ellis and Faulkner[19] noted cardiac enlargement by roentgenologic examination in 20 of 38 cases of anemia. The incidence of enlargement was greater in the group with hemoglobins below 50 per cent than in the group with hemoglobins above that level. Regression of enlargement followed elevation of the hemoglobin by appropriate treatment. Usually the cardiac silhouette reverted to normal size in three to twelve weeks.

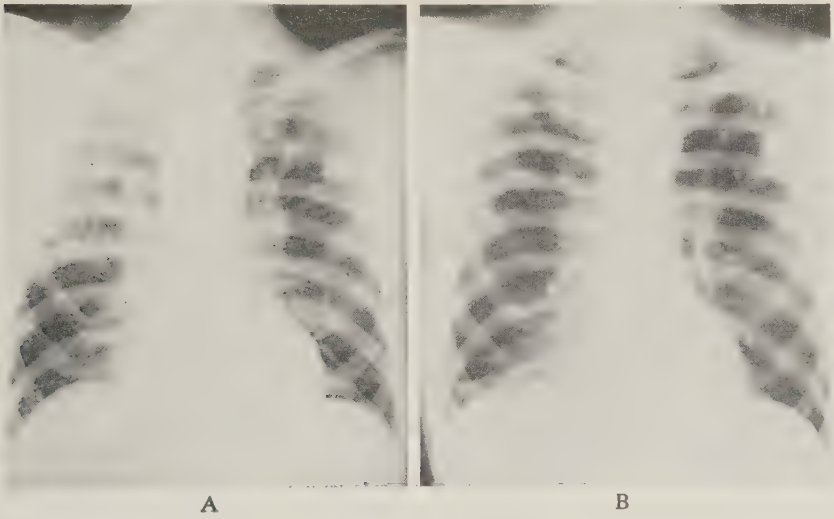


Fig. 79. *A*, Generalized cardiac enlargement associated with anemia, probably due to sulfonamides given for pneumonia of right upper lobe.
B, Recession of cardiac silhouette to normal in three weeks as anemia was corrected.

The *mechanism of cardiac enlargement* in anemia is uncertain. That the work of the heart may not be significantly enhanced has already been mentioned (p. 969). But further investigations in cases of very intense anemia may disclose a greater work strain than in the small series of cases studied by Stewart and his associates.[50] By exclusion it appears likely that the enlargement is due to the direct effect of anemia on the heart. This may result in myocardial inefficiency due to anoxia with a tendency to reduction in the cardiac output. The accumulation of blood in the chambers results in stretching of the fibers (dilatation), more forceful contraction and restoration of the needed output (p. 4). When an adequate cardiac output cannot be maintained by means of this dilatation (and perhaps subsequent hypertrophy), other compensatory mechanisms are invoked which eventually lead to the clinical syndrome of heart failure.

Cardiac Murmurs. The occurrence of cardiac murmurs in anemia has long been common knowledge. Anemia is the classic cause of the so-called functional cardiac murmur. The murmur associated with anemia is almost always systolic in time and heard either over the pulmonic area in the second or

third interspace to the left of the sternum or in the apical region.[19, 16] The murmur may be audible throughout the precordium, but then it is usually loudest in one of these two areas. Occasionally the systolic murmur is heard best over the aortic area. Radiation of apical systolic murmurs to the axilla or back in children has been described by Parsons and Wright.[42]

Of greater interest is the occasional appearance of a diastolic murmur in patients with anemia but without organic heart disease.[23, 14, 52, 27, 54] Such functional diastolic murmurs were heard in 6 of 39 patients with pernicious anemia studied by Goldstein and Boas.[27] The diastolic murmur has a blowing quality and may occur early in diastole and be localized to the left border of the sternum like the murmur of aortic insufficiency. But late diastolic or presystolic murmurs have also been described which are heard best at the apex and simulate the murmur of mitral stenosis.[27, 30] Despite the above-mentioned figures, it should be emphasized that diastolic murmurs are relatively rare in cases of anemia and have been heard only when the anemia is extremely intense and chronic, as in cases of sickle cell anemia and formerly in cases of pernicious anemia before specific therapy was available. Even in such cases the impression of a diastolic murmur may be created by a presystolic gallop or by a booming first sound as in hyperthyroidism.

The systolic murmurs heard in cases of anemia have been attributed to the speed of the blood flow and to dilatation of the ventricular chambers and atrioventricular rings. Diastolic murmurs have been explained as being due to dilatation of the pulmonic or aortic rings and to incomplete opening of the mitral valve associated with flaccidity of the papillary muscle.[42a] Both types of murmurs are variable in occurrence, appearing and disappearing with intensification or relief of the anemia, respectively.

Electrocardiographic Changes in Anemia. Many observers have reported no significant electrocardiographic changes[56] but others have reported consistent changes when the anemia is very intense.[53, 16, 7] The common abnormalities are:[33] depression of the ST segments and flattening or inversion of the T waves, findings suggestive of myocardial anoxia (see coronary insufficiency, p. 379). Similar ST deviations and alterations of the T wave attributed to coronary insufficiency have been observed after an acute loss of blood.[40, 48] Occasionally low voltage of the QRS complexes and prolongation of the P-R interval have been observed in cases of chronic anemia.

The electrocardiographic abnormalities usually disappear when the anemia is relieved.[19]

Heart Failure in Anemia. Dyspnea on exertion, tachycardia and palpitation, edema of the legs and cardiac enlargement occur commonly in severe chronic anemia and the combination of these symptoms and signs may be the basis of a mistaken diagnosis of congestive heart failure. Enlargement of the liver, as in cases of sickle cell anemia, may add to the resemblance. The absence of orthopnea, pulmonary congestion and venous engorgement and the finding of a normal venous pressure are the bases for excluding heart failure as the cause of the exertional dyspnea and the subcutaneous edema.

More study is desirable to illuminate the mechanism by which the various circulatory symptoms are initiated. Breathlessness occurs, as a rule, only with exertion. It may be that there is no pulmonary congestion at rest, but that it appears during exercise because the left ventricle is unable to handle

the increased venous return. Reduced arterial oxygen capacity, decreased oxygen saturation of the blood during effort and accumulation of blood lactic acid[8] may be contributory factors.

The cause of the edema is also obscure since it may be present despite a normal venous pressure. Possibly edema develops because of recurrent transient elevations of venous pressure following physical exertion during the course of the day. Hypoproteinemia may be a contributory factor in some cases. But Strauss and Fox[51] found no relation between edema and the plasma protein in their anemic patients. The degree of water retention and visible edema following salt ingestion in their cases varied inversely with the hemoglobin level. The venous pressure was normal before salt administration, but no mention is made of venous pressures following the ingestion of salt and the appearance of edema. Increased capillary permeability due to anoxia has also been suggested as a cause of edema in cases of anemia, but it is doubtful whether the degree of anoxia is sufficient to affect vascular permeability. Henry et al.[31] found evidence of increased capillary permeability as indicated by protein in capillary filtrate after venous occlusion of an extremity, but only when there was severe local anoxia as indicated by an oxygen saturation of the venous blood of 15 to 25 per cent or less. Comparable low oxygen contents of the venous blood occur in cases of severe anemia, but it is questionable whether these observations following venous occlusion can be applied to cases of anemia.

But actual heart failure may complicate severe anemia. Then dyspnea may occur at rest or on slight exertion; orthopnea or cardiac asthma appear occasionally. Râles at the bases of the lungs, hepatic enlargement and tenderness, subcutaneous edema, engorgement of the superficial veins and elevation of the venous pressure may all be present. In such cases it is a good rule to consider the likelihood that there is underlying cardiac disease although heart failure due to uncomplicated anemia has been noted.

Angina Pectoris and Anemia *(See also p. 361).* Angina pectoris has been observed with varying frequency in reported series of cases of severe anemia.[56, 43, 32] Pain of cardiac origin has been attributed to the lower oxygen content of the anemic blood. Intermittent claudication of the lower extremities, observed by Pickering and Wayne[43] in some extremely anemic patients, was attributed to similar anoxia of the calf muscles. The relation of anemia to angina pectoris has been discussed above (p. 361). It appears likely that anemia is only a contributory factor in the production of angina pectoris, usually in patients with underlying severe coronary arteriosclerosis. However, angina pectoris attributed to anemia per se has been reported.[18]

THE HEART IN SICKLE CELL ANEMIA

The described cardiovascular disturbances may occur in any longstanding intense anemia. But sickle cell anemia merits special discussion because:

(1) It is probably the commonest form of anemia observed today in which the degree of anemia is intense enough and of sufficient duration to produce cardiac symptoms;

(2) It is frequently complicated by symptoms which lead to a mistaken diagnosis of rheumatic fever, rheumatic or congenital heart disease or subacute bacterial endocarditis;

(3) It is occasionally associated with disseminated occlusions of the small pulmonary arteries which may result in pulmonary hypertension and chronic cor pulmonale[58, 35, 57] (p. 907).

The occurrence and frequency of cardiac manifestations in sickle cell anemia have been discussed by Anderson and Ware,[2] Klinefelter,[35] Winsor and Burch[57] and by Grover[28] among others. Winsor and Burch reported that 40 patients with heart disease due to sickle cell anemia were admitted to the Charity Hospital, New Orleans, in a single year and that heart disease due to this cause was more frequent among their Negro patients than that due to beriberi, myxedema, pernicious anemia or trauma.

Significant cardiac enlargement was present in at least 75 per cent of the cases of sickle cell anemia observed by Anderson and Ware[2] and in 95 per cent of those studied by Winsor and Burch.[57] Both the left and right ventricles are usually enlarged. The pulmonary salient of the cardiac silhouette is often prominent and the left border is straightened but the left atrium is not enlarged.[36, 39] Cardiac murmurs are heard in almost all cases. Most often they are systolic in type and heard over the mitral or pulmonary areas but systolic murmurs may be audible over any part of the precordium. Occasionally a diastolic murmur may also be audible over the mitral, aortic or pulmonic regions. The second pulmonic sound is often accentuated and may be split. Dyspnea is common but orthopnea and cardiac pain are rare. Hepatomegaly occurs frequently either as an intrinsic element of the disease or due to chronic passive congestion. Pulmonary infarction, pulmonary occlusion of the small arteries and pulmonary endarteritis, and pulmonary edema occur frequently. Electrocardiographic abnormalities are nonspecific and inconstant. Right axis deviation is rare despite the frequency of right ventricular dilatation and hypertrophy. Circulatory deaths are frequent, due to the sensitivity of patients with sickle cell anemia to anoxemia and shock, anesthesia and surgical procedures, infection and loss of blood.

Of special importance is the frequency with which cardiac findings due to sickle cell anemia are interpreted as being due to rheumatic or congenital heart disease.[35] There are several reasons for this error. Sickle cell anemia is the commonest reported cause of a functional diastolic murmur. Even when there is only a systolic murmur, organic heart disease is usually suspected because almost always significant cardiac enlargement is associated. An apical systolic murmur, often radiating to the axilla, an accentuated second pulmonic sound and cardiac enlargement with straightening of the left border of the heart on fluoroscopic examination strongly suggest rheumatic mitral valvular disease. This diagnosis seems to be supported by the history of attacks of pain in the extremities, especially about the joints which may be warm and swollen. In addition, fever is common during these attacks and leukocytosis is usual as in other hemolytic anemias. During the acute attacks of pain and fever, the finding of cardiac murmurs suggests that the above symptoms are due to recurrent acute rheumatic fever. Occasionally a diagnosis of subacute bacterial endocarditis is made because of the combination of fever with a cardiovalvular lesion. Occasionally, because of the youth of the patient with sickle cell anemia and because of the absence of a history of rheumatic fever, a diagnosis of congenital heart disease is made.

Diagnosis and Differential Diagnosis of Sickle Cell Anemia and Heart Disease. The possibility of sickle cell anemia should always be investigated in

any young Negro suspected of having organic heart disease. Sickling of the red blood cells should be sought also if cardiac murmurs and enlargement are discovered in any patient with a red blood count of less than 3,500,000 or a hemoglobin of less than 10 gm. Differentiation from rheumatic mitral disease may be aided by the absence of left atrial enlargement in sickle cell anemia, even when the pulmonary salient is prominent, and by the usual absence of right axis deviation. Salicylates are unlikely to relieve the joint pains and swelling. The finding of ulcers or the scars of ulcers near the ankles should also suggest sickle cell anemia in young colored individuals suspected of heart disease.

LEUKEMIA

Leukemic infiltrations of the heart were found in 43 of 123 fatal cases of leukemia.[61] In chronic forms of leukemia, associated with severe anemia, cardiac enlargement, systolic murmurs, tachycardia and palpitation, exertional dyspnea and subcutaneous edema may occur as in any other type of anemia. Occasionally there is frank evidence of congestive heart failure.[59] In such cases a diagnosis of heart disease and heart failure is usually made, without recognition of the causative leukemia.

Electrocardiographic changes in cases of leukemic infiltration of the heart include: sinus tachycardia, ST segment depression, T wave inversion in limb and precordial leads, prolongation of the P-R interval and premature contractions.[59]

Leukemic infiltrations of the pericardium, with pericardial effusion which is often hemorrhagic, have been described.[62] Roentgen ray therapy in a patient with heart block, presumably due to leukemic infiltrations, resulted in temporary disappearance of the conduction defect.[60]

CARBON MONOXIDE POISONING

Carbon monoxide poisoning, like anemia, reduces the oxygen transport capacity of the blood. In addition the formation of carboxyhemoglobin may interfere with the dissociation of the remaining oxyhemoglobin. Cardiac damage results from myocardial anoxia and depends on the severity and duration of the carboxyhemoglobinemia. Direct toxic damage to the heart muscle has also been claimed.[64] Concentrations of 25 to 35 volumes per cent of carbon monoxide in the blood are necessary before clinical manifestations appear. The importance of carbon monoxide poisoning as an industrial and domestic hazard is indicated by its position, second in frequency only to auto injuries, as a cause of accidental and suicidal death.

Clinical manifestations are most commonly referable to the central nervous system but our interest here lies particularly in the cardiac symptoms due to carbon monoxide poisoning. Such neurologic and cardiac symptoms may arise from prolonged exposure to concentrations of 0.01 to 0.02 per cent of carbon monoxide or they may represent the residua or sequelae from acute asphyxia due to exposure to much higher concentrations of the gas. It has been emphasized that chronic disease of the nervous system and heart may develop even when there is no loss of consciousness from the intoxication.

Experimental carbon monoxide poisoning of animals has resulted in vascular lesions consisting of small hemorrhages and perivascular infiltrations as well as focal areas of necrosis in the heart.[65, 77, 68] Similar myocardial necrosis

has been observed in humans who have succumbed following carbon monoxide intoxication.[74, 70, 71, 63] The lesions in the heart are confined essentially to the left ventricle and papillary muscle, and more particularly to the subendocardial region. These lesions resemble those observed following prolonged coronary insufficiency without coronary occlusion.[67, 69] Rupture of the heart following coal gas poisoning has been reported by Pulvertaft.[76] In some of the reported cases which concern older individuals it is difficult to apportion the relative influence of preexisting coronary arteriosclerosis and of carbon monoxide in the production of myocardial lesions.

Clinical evidence of myocardial involvement may appear promptly or several days after the acute intoxication by carbon monoxide. Or it may appear gradually after prolonged or repeated exposure. The chief symptoms are angina pectoris and cardiac irregularity.[80, 66, 72, 64, 73] Palpitation, tachycardia, precordial oppression or pain, exertional dyspnea and weakness have been noted. An attack of acute coronary occlusion has been attributed to carbon monoxide poisoning.[64] Auricular fibrillation may be precipitated. When cardiac enlargement is observed, the presence of some preexisting cardiovascular abnormality is likely. The relative importance of such underlying disease as the cause of the patient's cardiac symptoms and signs may present a medicolegal problem if the patient attempts to collect insurance, compensation or personal damages following carbon monoxide poisoning. As a rule, symptomatic recovery from the cardiac disturbances is complete within a few weeks or months but chronic organic heart disease may result from carbon monoxide intoxication according to Beck and Suter.[64]

Electrocardiographic changes have been repeatedly observed but they may be absent even when the carbon monoxide poisoning is severe enough to be fatal.[75, 78] The most frequent abnormalities are slight ST interval depressions and lowering or flattening, rarely inversion, of the T waves, the so-called pattern of coronary insufficiency.[79, 78] Paroxysmal auricular fibrillation and premature beats are not rare. Occasionally lowering of the voltage of the QRS complexes, intraventricular block or prolongation of the P-R interval has been observed. As a rule the electrocardiogram reverts to normal within two months, but occasionally the abnormalities persist.

POLYCYTHEMIA

Polycythemia (erythremia) may be a consequence or a cause of cardiovascular disease. Polycythemia is a characteristic finding with certain congenital cardiac lesions such as the tetralogy of Fallot, in which there is a large venous-arterial shunt. It is also observed in cases of severe chronic pulmonary heart disease (Ayerza's syndrome) and not infrequently in cases of very severe chronic heart failure such as that associated with tricuspid stenosis (p. 620). In the presence of polycythemia, the possibility of these causative forms of heart disease should be considered. In all of these examples the polycythemia is viewed as a compensatory response to a sharp reduction in the oxygen saturation of the arterial blood.

Polycythemia, Vascular Thromboses and Coronary Disease. Polycythemia is frequently complicated by circulatory disturbances due to increased viscosity and slowing of the blood. Arterial and venous thromboses occur particularly in the cerebral and peripheral vessels.[89] Not infrequently also, polycythemia is associated with thrombosis of a coronary artery and myocardial infarction.

It is likely that in such instances the polycythemia is a contributory cause and not merely coincidental with the coronary occlusion. The occurrence of coronary thrombosis in cases of polycythemia vera has been documented by Christian,[84] Oppenheimer,[90] Boyd[82] and by Dameshek and Henstell[85] among others. Tinney, Hall and Giffin[91] found clinical evidence of coronary disease in 10 (6 per cent) of 163 cases of polycythemia vera. Four of these patients with coronary disease had angina pectoris. One of these, a woman forty-eight years old, suffered a coronary occlusion in the absence of hypertension or diabetes.

Polycythemia and Absence of Heart Failure. Polycythemia is associated with a greatly augmented blood volume which might be considered to produce an unusual load on the heart and congestion of the viscera. Nevertheless, heart failure is a rare complication except when there is associated myocardial infarction or hypertensive and arteriosclerotic heart disease. The increased blood volume is due essentially or exclusively to the increased cell volume and there is a consequent increase in viscosity and a corresponding slowing of the blood stream. The venous return and cardiac output are normal,[88, 87, 81] since the effect of the increased blood volume on the venous return is neutralized by the slowing of the circulation. The work of the heart is unaltered except when there is hypertension. Similarly cardiac enlargement is notably absent when there are no complications.[83] (See also p. 103.)

Polycythemia and Hypertension. The combination of polycythemia vera and hypertension has been segregated as a separate syndrome[86] but it is more probable that the hypertension is a coincidental abnormality. Brown and Giffin[83] found the average blood pressure in 14 cases of polycythemia vera to be 138 mm. Hg systolic and 90 diastolic. Tinney and his associates[91] found the systolic blood pressure above 150 mm. Hg in about 40 per cent and above 180 in about 10 per cent of their 163 cases of polycythemia vera. It is uncertain whether these blood pressures exceed those to be found in subjects of similar age groups without polycythemia vera.

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44

TRAUMATIC HEART DISEASE

Traumatic heart disease includes the anatomic lesions and functional disturbances of the heart which result from external injury or from an intense, unusual physical exertion. According to the causative mechanism, cardiac trauma may be classified as follows: (1) penetrating lesions of the chest wall; (2) nonpenetrating lesions; (3) physical strain. In addition there are instances of so-called spontaneous rupture, perforation or tear of a cardiac structure, in which physical strain may be a significant contributory factor.

HEART DISEASE DUE TO PENETRATING LESIONS

Since Rehn[83] successfully sutured a stab wound of the human heart in 1896, numerous similar reports have attested to the curability of penetrating cardiac lesions when the diagnosis is made early and proper surgical repair instituted rapidly. In this country interest in penetrating wounds of the heart has been stimulated in great measure by the reports of Bigger,[12] Elkin,[28] Beck,[11] and Harken.[39]

In civilian life, penetrating wounds of the heart result usually from stabbing by knife and occasionally from bullet wounds. Other sharp instruments, such as the ice-pick, stiletto or needle[46, 36] may be responsible. Needle wounds of the heart may occur accidentally or during pericardial aspiration or intracardiac injections of epinephrine.[8] In warfare, penetrating cardiac injuries are usually due to bullet wounds or shell fragments. Penetrating wounds of the heart may result indirectly when shattered glass or splinters perforate the chest wall in auto or plane accidents or when the heart is torn by the sharp ends of broken ribs.

The usual site of entrance of the penetrating object is the precordium, but occasionally cardiac injury results from penetrating wounds elsewhere in the chest wall, or even in the neck, abdomen or pelvic region. Of special interest are the wounds of the heart caused by foreign bodies, such as needles and shell fragments, which lodge in a peripheral vein and reach the cardiac chambers by way of the venae cavae or pulmonary veins.[92, 93, 40, 41] Sharp foreign bodies which accidentally reach the esophagus may perforate its wall and thence lacerate or perforate the heart. McCartney and Drummond[72] reported a case of gunshot wound of the liver in which the foreign body entered an hepatic vein, reached the right side of the heart and lodged in the right ventricle.

Pathology

Any portion of the heart may be injured by the penetrating object. Injury to the pericardium alone may give rise to a fibrinous pericarditis or pericarditis with effusion. The concomitant introduction of infectious agents may lead to a purulent pericarditis. The anterior surface of the right ventricle is the most commonly involved portion of the heart, but the right atrium and the left ventricle are also wounded frequently. The intrapericardial portions of the great vessels may be perforated. Injury to a coronary artery, especially the anterior descending branch of the left coronary, is a common complication of cardiac wounds.[77, 37, 60, 9, 99] Although uninjured, the coronary artery may have to be ligated during cardiac suture. Perforation of the myocardium, great vessels or coronary artery is followed usually by hemopericardium. Coronary arterial perforation and thrombosis may be associated with myocardial infarction. The interventricular septum may be injured [20, 27, 65] and the auriculoventricular conduction system impaired or interrupted. Occasionally, valvular cusps, chordae tendineae or the papillary muscles are perforated or torn with consequent valvular insufficiency and cardiac strain.

A ventricular or auricular thrombus may develop at the site of injury or at the site of lodgement of a foreign body. Cerebral, pulmonary or peripheral embolization may result from such mural thrombi or from passage of migrating foreign bodies. In the majority of cases the foreign bodies lodge in the pericardium or myocardium without further migration.[92] Occasionally such a foreign body causes local myocardial injury, hemorrhage and hemopericardium, local myocardial abscess or a purulent pericarditis or mediastinitis.

Clinical Features

The symptoms and signs associated with penetrating lesions of the heart are caused by hemorrhage, acute cardiac tamponade, fibrinous or suppurative pericarditis, contusion or infarction of heart muscle, valvular rupture or embolism. Death may occur suddenly from ventricular fibrillation or ventricular standstill. If treatment is delayed, death often ensues in a few hours after the injury, due to cardiac compression or exsanguination.

Usually the patient when first seen presents some degree of shock from loss of blood, cardiac compression or both. He may be stuporous or unconscious, confused or delirious. Tachycardia, a weak rapid pulse, tic-tac heart sounds (embryocardia), restlessness and cold moist skin are noted commonly. Pallor, a fall in hemoglobin and leukocytosis result from an acute, massive loss of blood. Sometimes circulatory insufficiency is due not to loss of blood or cardiac compression but to a reflex arteriolar dilatation and consequent reduction in blood pressure.[73]

With the rapid development of hemopericardium, the heart is compressed, diastolic filling is restricted, the venous inflow is retarded and the cardiac output is sharply curtailed.[97] These physiologic disturbances are expressed clinically by a falling blood pressure and pulse pressure, a rising venous pressure, a quiet heart (small excursions fluoroscopically), and a small and paradoxical pulse. There may or may not be dyspnea or cyanosis. Eventually the frank picture of circulatory shock unfolds. Not infrequently the bleeding is moderate and slow and many hours may elapse before there is evidence of cardiac tamponade or other signs of cardiac injury.

Pericarditis may be signalled by precordial pain, a friction rub, or by signs of pericardial effusion (p. 507). If infection develops, fever appears and there are progressive signs of cardiac tamponade due to purulent pericarditis.

Valvular tears or rupture of the chordae are denoted by loud, rough murmurs and by progressive cardiac insufficiency. Injury to a coronary artery usually causes hemorrhage, hemopericardium and cardiac tamponade. Subsequent spontaneous occlusion or ligation during surgical repair may cause myocardial infarction, sometimes with classic electrocardiographic signs of infarction, but without apparent clinical symptoms of that condition.

Embolization with resultant hemiplegia, pulmonary infarction or acute cor pulmonale, or peripheral vascular occlusion and gangrene may result from local mural thrombi at the site of the penetrating lesion or more often from migrating intravascular foreign bodies.

Roentgenologic examination may reveal an enlarged cardiac silhouette due to hemopericardium, but often the hemorrhagic effusion is too small to affect the size of the cardiac shadow. The fluoroscopic examination, which is of special value, discloses an almost complete absence of pulsation during the stage of cardiac tamponade. It is also essential for the recognition and localization of intravascular and intracardiac foreign bodies. In addition the roentgenologic examination may disclose associated intrathoracic lesions such as fractured ribs, hemothorax, pneumothorax and extensive pulmonary hemorrhage.

The Electrocardiogram. Electrocardiographic tracings from patients with stab and gunshot wounds of the heart have been published by Cole,[21] Davenport,[24] Bates and Talley,[7] Koucky and Milles[59] and others, but the most comprehensive reports are those of Wood,[98] Solovay, Rice and Solovay,[90] Herve and Forero[43] and Noth.[76] In the first hours after the injury and before operation there is definite evidence of cardiac involvement in most cases. This evidence consists of electrocardiographic signs of pericarditis, bundle branch block or of myocardial infarction. Precordial leads may disclose significant abnormalities when none are present in the standard leads.[23] However, minor RST deviations and T wave alterations are nonspecific and may be observed in thoracic wounds without cardiac injury.

In the first few postoperative days, the electrocardiogram usually depicts changes associated with pericarditis, whatever the site of the wound and whether or not a coronary artery has been injured or ligated during suture. A serofibrinous pericarditis is an almost constant sequel of surgical exploration of a cardiac wound. There are characteristic RT elevations in leads I and II or in all standard leads. Wood[98] refers to this as the T_2 type because the RT segment elevations are greatest in lead II, whereas in acute myocardial infarction the RT elevation is greatest in lead I (T_1 type) or in lead III (T_3 type). As in other forms of pericarditis, the elevated RT segment is concave upward while in myocardial infarction it is convex upward.

Gradually after three or more weeks the T waves are flattened and later become fully inverted. The T wave inversions may persist for many months or years,[76] but usually they revert to normal after three months. Definite localizing electrocardiographic signs directly due to a left or right ventricular injury may be seen very early, before they are masked by the pericarditis or after three or more months when the pericardial signs have disappeared.

These localizing signs consist of QT patterns similar to those seen with ventricular infarcts or occasionally of evidence of bundle branch block. When an injury or suture occludes the anterior descending branch of the left coronary artery, there may be a Q_1T_1 pattern due to infarction of the anterior wall of the left ventricle or possibly to a left ventricular wound without coronary artery involvement. Multiple precordial leads may reveal localizing signs as evidenced by T wave inversion in one or more leads. The important point to emphasize is that electrocardiographic changes represent the most constant evidence of cardiac involvement in penetrating chest wounds; their subsidence or persistence may be a reliable index of the functional or organic basis of symptoms which remain for a long time after operation. They are less reliable for localization of the exact site of injury.

Diagnosis

It is usually simple to diagnose a penetrating wound of the heart if due regard is given to the history of the injury, the site of entrance of the penetrating object in the precordial region and the clinical manifestations of cardiac tamponade. Greater diagnostic difficulty is encountered when the penetrating object reaches the heart through some point removed from the precordium. Then cardiac involvement may be suspected from symptoms and signs of hemopericardium (see pericarditis with effusion, p. 507, and cardiac compression, p. 508), or from loud murmurs, a pericardial rub, heart block or congestive heart failure. The association of a stab or gunshot wound of the chest with electrocardiographic changes suggesting myocardial infarction or pericarditis is also diagnostic of cardiac injury. The presence of ST and T wave abnormalities following a penetrating chest wound denotes cardiac injury; concordant ST elevations and T wave inversions in leads I and II or in all standard leads denote pericarditis not involving the coronary artery; reciprocal ST elevation and depression in leads I and III with inversion of only T_1 or T_3 denote coronary artery injury.[6]

Prognosis and Treatment

Many patients succumb from exsanguination, shock and possibly ventricular fibrillation or cardiac standstill before reaching the hospital.

Operative intervention is required in most cases of penetrating wounds of the heart.[28, 75, 85] In recent years there has been a trend toward conservative (nonsurgical) therapy in the milder cases.[29, 12, 14] In general, conservative therapy is maintained when hemorrhage is moderate or slight, when there is no evidence of cardiac tamponade or when the signs of tamponade diminish following medical treatment. Operation is indicated when there is severe, persistent hemorrhage (free pericardiopleural communication) and when there is evidence of cardiac tamponade which is not relieved by pericardial aspiration or recurs rapidly after aspiration.

When the patient is first seen, measures are instituted to counteract hemorrhage and shock. The use of the Trendelenburg position, the administration of morphine and atropine and sometimes of epinephrine have been recommended. Transfusions of compatible whole blood should be given, or plasma or other fluids may be administered by venoclysis if there is a delay in obtaining whole blood. Intravenous infusions may improve the cardiac output and

clinical condition even in the presence of cardiac tamponade.[22, 97] The thorax should be examined for the presence of pneumothorax, hemothorax or splashing sounds indicative of a free pericardiopleural communication. Determinations of the blood pressure and observations of the cervical veins and of the radial pulse should be made during preparations for operation.

An anesthetic is usually employed, but in cases of extreme urgency, if the patient is unconscious and respirations have ceased, the heart has been exposed without anesthesia while artificial respiration was performed. If possible, the heart is approached extrapleurally through a left anterior thoracic incision. But often it is necessary to incise the pleura and occasionally better exposure is obtained by an incision to the right of the sternum. Ligation of the internal mammary or of an intercostal or coronary artery may be required for the control of bleeding. Bleeding from the heart or from a coronary artery is usually associated with an intrapericardial clot which should be evacuated. Beck[11] has suggested that ventricular hemorrhage be controlled by placing the index finger over, but not into, the cardiac wound while the heart is steadied by an apical suture which is held by the first and third fingers. He then places control sutures on either side of the finger over the wound, crosses and holds them while the wound is being repaired. Auricular wounds are controlled by clamps until they can be repaired. Recently hemorrhage from the cardiac atria has been controlled by means of the gelatin sponge.[48]

If the outstanding clinical signs are those of cardiac compression, the pericardium should be aspirated, preferably by the costoxiphoid approach. Recovery may follow paracentesis even when there is massive hemopericardium.[80] If tamponade recurs following temporary relief, aspiration should be repeated. However, operative intervention is indicated if the signs of compression are not relieved or recur promptly or repeatedly. Although recovery has been reported following nonoperative treatment,[80, 14] cardiac tamponade should not be allowed to persist for many hours because of the danger of the irreversible changes of shock, such as renal insufficiency.[91]

If a foreign body in the heart is presented soon after the accident, prompt removal is advisable in order to avoid the danger of cardiac erosion, hemorrhage, rupture or infection and the possibility of embolic vascular occlusion.[25] In the absence of symptoms the foreign body may be left in situ if continued observation discloses no change in its position. If the foreign body is discovered accidentally, weeks, months or longer after the injury, it is undesirable to attempt removal if there is evidence that the object is fixed by scar tissue. But an exploratory operation may be necessary if the patient has complaints which appear to be referable to the foreign body, e.g., pain, or a cardiac neurosis develops because of the presence of pain. Many instances have been reported of the successful removal of foreign bodies including bullets, shell fragments and needles.[36] Harken[39] reported no deaths in a series of 134 patients operated for foreign body in the heart or great vessels.

The results of surgical operations for penetrating wounds of the heart have been reported by Ramsdell,[81] Bigger,[12] Elkin[28] and others.[15, 70, 85] Bigger[12] estimated the mortality of cardiac suture to be about 30 per cent. Elkin[28] obtained recoveries in 22 of 38 patients on whom he operated for cardiac wounds. Complete recovery may follow even when a major coronary artery must be ligated.[99] Cardiac infarction need not follow. Follow-up studies of

119 cases of cardiac wounds in which the patient survived operation disclosed restoration of function that was complete in 77.3 per cent, fair in 22.7 per cent and poor in 1.7 per cent.[44] Ligation of the anterior descending branch of the left coronary artery did not influence the result. The site of the sutured wound heals to a firm scar. A series of such cases in which the heart was later studied histologically has been collected and reported by Gronwald.[37]

NONPENETRATING INJURIES OF THE HEART

Increasing recognition has been given in recent years to the occurrence of cardiac damage following a nonpenetrating blow to the chest wall. Our knowledge of these nonpenetrating cardiac lesions has been especially enhanced by the studies and reviews of Barber,[4] Beck,[10] Warburg[96] and others. The following discussion is designed to call attention to the occurrence of cardiac damage from blunt injury to the chest wall, but at the same time to caution against attributing to a preceding trauma a host of unrelated cardiac disturbances which are the consequences of the natural course of underlying, independent organic heart disease.

Contusion or rupture of the heart following a blow to the chest was demonstrated experimentally in rabbits and dogs by Külbs,[61] Schlomka,[86] and by Kissane, Fidler and Koons.[55] By controlled measured forces which struck but did not penetrate the chest wall they were able to cause subepicardial and subendocardial myocardial hemorrhages and hemopericardium, cardiac necrosis and heart failure, arrhythmias and various electrocardiographic abnormalities, and sudden death due to ventricular fibrillation or cardiac standstill. More severe injuries including cardiac rupture and lesions resembling myocardial infarction were noted when the blows were applied directly to the exposed hearts of animals.[74, 17]

Support for the concept of cardiac disease following blunt injuries of the chest wall is also provided by numerous clinical and pathologic observations.[95, 52, 94, 10, 4, 96] Necropsy studies had long ago demonstrated that fatal rupture of the heart can follow a severe blunt injury to the chest.[95] But only recently has emphasis been placed on the frequency of less severe cardiac injuries with asymptomatic recovery or of survival with a variety of transient or persistent and serious cardiac symptoms. In an analysis of 175 cases of nonpenetrating wounds of the heart Bright and Beck[17] found 152 instances (87 per cent) of death from cardiac rupture (proven by necropsy), 11 instances (6 per cent) of death from myocardial failure, and only 12 instances (7 per cent) of recovery. Beck[10] believed that the percentage of recoveries was much higher but that there was a failure to recognize or a fear to diagnose clinical heart disease due to cardiac contusion.

In some cases the demonstration of hemopericardium by paracentesis, following nonpenetrating chest trauma, strongly supports the clinical diagnosis of cardiac contusion. More often, in reported cases in which transient or persistent clinical manifestations are interpreted as evidence of myocardial damage or of acute or chronic heart failure due to cardiac contusion, there is great uncertainty as to the accuracy of the diagnosis or interpretation. In particular, it seems to me that neurocirculatory asthenia or cardiac neurosis, independent coincident cardiovascular disease, reflex cardiovascular disturbances following trauma and its emotional concomitants, and pulmonary embolism have been interpreted in different cases as heart disease due to cardiac contusion.

Etiology

A frequent cause of nonpenetrating cardiac injury is the recently publicized steering wheel accident.[28, 10] The driver's chest is pinned against the steering wheel when the forward momentum of the car is suddenly arrested. Severe cardiac injury or rupture of the heart often follows crushing chest accidents when an auto, train or other vehicle runs over the prostrate body. Falls from a great height result in similar cardiac damage, often associated with serious injuries in other parts of the body. Direct blows to the anterior chest wall by a baseball, golf or tennis ball traveling at high speed, by heavy falling or swinging objects which strike at great velocity, fist blows, kicks by a horse or other powerful animal, and compression of the chest between two moving objects are among other causes of nonpenetrating cardiac trauma. In battle experience, blast injuries form an additional causative mechanism.

As a rule the nonpenetrating force strikes over the precordium, but cardiac injury occasionally follows blows to the posterior thorax, abdomen or lumbar region.[88] Serious contusion and even rupture of the heart often occurs without any significant visible external injury of the chest wall and without fracture of the ribs.[13, 38, 17, 96, 82] In fact, in the series of 250 nonpenetrating chest injuries reported by Arenberg,[2] the greater cardiac damage occurred among the cases without rib fracture. Conversely, bilateral multiple fractured ribs were usually unaccompanied by cardiac damage. And among the 152 cases of ruptured heart following nonpenetrating injuries of the chest assembled by Bright and Beck,[17] evidence of fractured ribs was found only in 58.

Clinical and experimental observations suggest that blunt injury is more likely to damage the diseased heart than the normal one. Külbs and Strauss[63] found that the hearts of rabbits previously rendered atherosclerotic and the hearts of dogs intoxicated with excessive doses of digitalis or thyroxin were more readily injured by blunt force applied to the chest than were the normal hearts of these animals. It may be that diseased human hearts are similarly more susceptible to nonpenetrating blows, but preexisting cardiac disease is by no means as important a predisposing factor as in the cases of cardiac injury following unusual and severe physical strain.

Cardiac Strain. In discussions of nonpenetrating cardiac trauma there is often a lack of distinction between lesions produced by blunt injuries to the chest wall and those due to overstrain of the heart. Cardiac strain refers to the anatomic lesions and functional disturbances which result from some intense and unusual physical effort. Because this type of traumatic heart disease is frequently involved in compensation and other medicolegal problems, and because it rests on less scientific foundation than the type due to blunt injury of the chest wall, it should be distinctly segregated.

The Effects of Unusual Effort on the Normal and Diseased Heart. There is always uncertainty about reported instances of damage to the normal heart due to physical effort. Doubt usually surrounds the claim that the heart was previously normal. When arrhythmias follow a physical strain there is also a question of coincidence, for arrhythmias not infrequently arise in the normal heart without unusual effort or other apparent cause.

The so-called "athlete's heart," i.e., cardiac dilatation and hypertrophy formerly attributed to athletic activity, is now believed to be the consequence of independent rheumatic, congenital or syphilitic heart disease. Transient

cardiac enlargement occurs occasionally during strenuous physical exertion, but this is a reversible compensatory dilatation (p. 10) which disappears promptly with cessation of the activity.[26, 84] There are no well authenticated cases of congestive heart failure developing as a result of a physical effort in an individual with a normal heart. Disorders of rhythm, including premature beats, paroxysmal tachycardia and even auricular fibrillation, may first appear in a normal heart after strenuous exertion; much more commonly this sequence is observed when there is underlying cardiac disease. Rarely is a normal valve or chorda tendinea ruptured by physical exertion. Physical effort, especially in combination with emotional stress, commonly induces a paroxysm of angina pectoris, but only in subjects with advanced coronary arteriosclerosis or other disease diminishing the coronary reserve. The precordial oppression sometimes experienced by normal subjects during a prolonged race and before "second wind" may represent angina pectoris due to functional coronary insufficiency, but this disappears rapidly and recurs only with very unusual and strenuous exertion.

In the previously diseased heart, the strain of physical effort apparently may induce the disorders of rhythm already mentioned, rupture of a valve, chorda or papillary muscle, a paroxysm of angina pectoris and occasionally congestive heart failure. Severe prolonged exertion is theoretically capable of causing myocardial necrosis without coronary occlusion but there is great controversy as to whether it ever precipitates the occlusion itself (p. 407). Physical effort, in contrast with blunt injury to the chest wall, is not the cause of pericarditis, myocardial contusion or rupture. The specific cardiac lesions attributed to nonpenetrating injuries and to cardiac strain are discussed under Pathology.

Pathology of Nonpenetrating Cardiac Trauma

The pericardium and myocardium are most frequently injured by blunt injuries of the chest; the valves or their attachments are most commonly said to be torn by an unusual physical effort.

The Pericardium. Fibrinous pericarditis and hemopericardium result from nonpenetrating trauma, the latter much less frequently than after penetrating wounds. Contusion of the pericardium and epicardium is probably fairly common but is easily overlooked in nonfatal cases because of the paucity or absence of physical signs and symptoms. Pneumopericardium and hydropericardium have been reported.[89] Occasionally a nonpenetrating cardiac trauma stirs up a tuberculous or purulent pericarditis.

The Myocardium. The myocardium may be merely bruised (cardiac contusion), it may be partially lacerated or it may suffer a through and through perforation involving the wall of one or more chambers or of the septa (rupture of the heart). Bright and Beck[17] assembled 152 cases of rupture of the heart, in which the various chambers were involved with almost equal frequency, but in which the left ventricle and right atrium predominated. In addition, in this series the interventricular septum was perforated 13 times, the interatrial septum once, and multiple chambers 13 times. The papillary muscle may be ruptured by blunt injury to the chest as in the cases reported by Kleberger[57] and by Glendy and White.[35] Rupture of the heart may occur promptly after the injury, but there is often an interval of five to fifteen days before the hemorrhagic, disorganized, softened area perforates.[78, 96]

Rupture of the heart is a fatal consequence of the most intense crushing injuries of the chest wall. Of greater clinical interest and importance are the less severe contusions characterized by less extensive subendocardial and subpericardial myocardial hemorrhage and dissolution of tissue, often associated with overlying local pericarditis. As in the experimentally induced cardiac contusions,[74] these bruised areas of heart muscle may heal with the formation of a firm scar, indistinguishable from the scar of a cardiac infarct due to coronary artery occlusion.[45] That cardiac contusion may be followed by cardiac aneurysm is suggested by the report of Joachim and Mays.[50] Endocardial thrombosis and cerebral embolism may also follow contusion of the heart.[78a]

Coronary Artery Disease. The above-mentioned form of myocardial hemorrhage, necrosis and scarring caused by a blunt chest injury (contusio cordis or commotio cordis) should be distinguished from the cases of myocardial infarction secondary to arteriosclerotic coronary occlusion in which the coronary occlusion is believed to have been precipitated or accelerated by the strain of some physical exertion. The possible causal relationship of arteriosclerotic coronary occlusion to physical strain has come to assume medicolegal importance, particularly in connection with insurance and workmen's compensation. This problem has been discussed under the heading of etiology of acute coronary occlusion (p. 407).

In many reported cases the sequence of events after a severe and unusual physical strain strongly suggests that the strain in some way initiated or accelerated the coronary artery occlusion and the consequent infarct.[79, 16] There is no doubt that the fundamental cause of the occlusion in these cases is atherosclerosis; but the unusual effort is believed to precipitate the occlusion either by causing intimal hemorrhage in the atherosclerotic plaque or by some other undetermined mechanism. Master[71] and his associates have marshalled considerable evidence to refute these interpretations but admit that in 2 per cent of a large series of cases of coronary artery occlusion, there was a chronologic if not causal relation to unusual exertion. Since about 500,000 cases of coronary occlusion occur annually, at least the possibility that effort is a precipitating factor must be considered in 10,000 cases. Certainly this relationship should be given credibility in relatively few instances of this potential group.

Occasionally a strenuous or unusual exertion occurs in a person with severely narrowed (atherosclerotic) coronary arteries. The exertion may so intensify the coronary insufficiency relative to the needs of the myocardium that myocardial anoxia and necrosis develop, usually in the subendocardium of the left ventricle and papillary muscles. Such cardiac necrosis without recent coronary occlusion[31] may present a clinical picture identical with that of acute coronary thrombosis; there may be symptoms of angina pectoris with corresponding electrocardiographic changes, or there may be no detectable clinical manifestations.

Finally there are instances in which a blunt injury to the chest wall caused not a cardiac contusion but purportedly precipitated an arteriosclerotic coronary artery occlusion and myocardial infarction.[87, 96, 54, 69] Great care is necessary in interpretation. Thus in the case reported by Kienle[54] of a forty year old man who fell while skiing and then experienced the typical clinical course of coronary occlusion and posterior wall infarction, one must consider not only the possibility of coincidence but also the possibility that the occlusion was the cause, not the consequence, of the fall. In some instances the youth of the patient is used to support the interpretation that the blunt chest injury

and not the natural course of preexisting disease was responsible for the coronary occlusion. The report of MacDonald[69] concerns a twenty-one year old man who was struck on the chest by a soft ball. There was clinical and electrocardiographic evidence of myocardial infarction. Postmortem examination disclosed old and recent coronary occlusions. However, recent studies have amply demonstrated that the premature occurrence of advanced coronary atherosclerosis is no rarity.[30] In clinical reports without autopsy studies it is always difficult to differentiate between cardiac contusion following blunt chest injuries and coincident or causally related coronary artery occlusion.

Valvular Lesions. Rupture of a valve or of chordae tendineae may follow nonpenetrating injury to the chest or severe physical strain. More often the affected valve is the seat of preexisting rheumatic, syphilitic, congenital or arteriosclerotic disease, but normal valves have also been lacerated or perforated by these forms of indirect trauma.

In experimental cardiac contusions in animals, valvular hemorrhages were sometimes seen but no ruptures.[61] Barié[5] found in his experiments with human hearts post mortem that extremely high pressures were required to rupture a valve. Nevertheless there are apparently well authenticated cases of rupture of normal human valves both as a result of physical exertion and nonpenetrating injury to the chest. Fourteen such cases were assembled from the literature by Adam[1] who also reported a case of his own. Howard[47] reported an instance of traumatic aortic insufficiency due to rupture by strain of a normal aortic valve, while Kissane, Koons and Fidler[56] described a proven case of rupture of the aortic valve due to crushing injury to the chest following an explosion.

The aortic valve is most commonly affected;[47, 19] the mitral valve is next in frequency of involvement while the pulmonic and tricuspid valves are torn more rarely. The greater frequency of the left-sided valvular injuries may be attributed both to the higher intracardiac pressures on that side and to the greater frequency with which these valves are the site of underlying disease. Injuries to the mitral valve include tears of the cusp itself or more commonly rupture of chordae tendineae or occasionally of a papillary muscle. Rupture of apparently normal mitral chordae following severe exertion was reported by Frothingham and Haas.[32] Rupture of the mitral chordae may occur spontaneously, usually as a result of underlying bacterial endocarditis. Bailey and Hickam[3] reported 7 cases of spontaneous rupture of mitral chordae tendineae in which rheumatic endocarditis was the underlying condition. In such cases of spontaneous rupture of diseased valves, the actual event may be attributed properly or improperly to some physical effort. In the cases reported by Bailey and Hickam[3] the histories failed to indicate that vigorous exertion or external trauma was of primary importance in the rupture.

Other Cardiac Lesions Attributed to Indirect Trauma. Acute and subacute bacterial endocarditis, suppurative myocarditis and pericarditis have each at times been ascribed to commotio cordis. In these cases the injury is credited with creating a locus minoris resistentiae, lighting up a latent infection or permitting the entrance of bacterial agents which then produce bacterial endocarditis in a heart predisposed by an underlying valvular lesion.[34] However, in some of the recorded cases the clinical diagnosis of endocarditis is questionable and in all the cases of subacute bacterial endocarditis the insidious onset of the disease makes it impossible to relate it accurately in point of time to the trauma. Sometimes traumatic lesions in distant parts of the body or in

the lungs, pleura or mediastinum lead to infections which later extend to the pericardium or heart.

Clinical Features of Nonpenetrating Cardiac Trauma

Rupture of the heart is rapidly fatal but occasionally not until the second week after the injury. On the other hand mild cardiac contusion may be asymptomatic. When symptoms do develop, they may appear immediately or after a variable interval of days or even weeks. There may or may not be a loss of consciousness even after serious blows to the chest wall.

Chest pain is probably the commonest complaint after nonpenetrating trauma. This may arise in the traumatized chest wall, the pleura, pericardium or the heart. A persistent or recurrent dull ache in the precordium or apical region may be a symptom of cardiac neurosis following trauma. Occasionally a severe or unusual exertion or a nonpenetrating chest injury precipitates the first attack of typical angina pectoris.[68] The angina pectoris may be due exclusively to cardiac contusion but as a rule there is underlying arteriosclerotic coronary artery disease or syphilitic coronary ostial narrowing.[58] Prolonged cardiac pain with all the other features of acute coronary thrombosis has been recorded following cardiac contusion.[66]

Weakness is a frequent complaint after cardiac contusion or after valvular rupture. It usually subsides after a brief period but may persist, especially if cardiac failure develops.

Palpitation may result from tachycardia, arrhythmia or exaggerated awareness of the normal heart beat.

Disorders of rhythm and rate are among the commonest reported manifestations of nonpenetrating cardiac trauma. *Tachycardia* is common but sinus bradycardia has also been recorded.[62] Usually the tachycardia is transient but may persist in the presence of cardiac neurosis. Occasionally ventricular tachycardia and ventricular fibrillation have been noted. *Auricular fibrillation,* usually transient, is the commonest important arrhythmia associated with nonpenetrating cardiac trauma or severe effort.[42] It may occur in the previously healthy heart.[52, 67, 82] In Warburg's[96] series there were at least 32 instances of auricular fibrillation or about one third of the entire group. In nearly half of the cases the arrhythmia persisted. Auricular flutter has also been recorded.[51] *Heart block,* incomplete[94] or complete,[64, 33, 20] has been observed on occasion. This may be due to traumatic hemorrhage into the conduction tissues. But unless the subject has been examined previously, congenital heart block is difficult to exclude (p. 301).

Congestive heart failure commonly follows severe injuries to the heart. It may start rapidly after the trauma with progressive acute pulmonary edema, or it may evolve more slowly from symptoms of mild left heart failure to advanced left- and right-sided congestive heart failure. But in cases of rupture of a valve or its chordae, signs and symptoms of heart failure may not appear for many months. Heart failure may also result from prolonged paroxysmal tachycardia or auricular flutter or fibrillation and rapid ventricular rate. When there are only a few symptoms such as dyspnea and fatigability, the diagnosis of heart failure should be differentiated from cardiac neurosis and pulmonary injuries.

Enlargement of the heart is usual in those individuals who develop heart failure after cardiac trauma. But hemopericardium may simulate cardiac

enlargement and by causing cardiac tamponade may produce symptoms of congestive heart failure.

Angina pectoris and manifestations of cardiac infarction have been mentioned. *Sudden death* may occur after cardiac trauma with or without preceding symptoms of angina pectoris.

Distinctive clinical features may be produced by *rupture of valves* or by *pericarditis and hemopericardium*. Rupture of a valve or chorda tendinea may be characterized by sudden onset of precordial pain, dizziness, weakness, breathlessness, palpitation or shock. The diagnostic feature is a very loud, coarse precordial murmur. In aortic lesions, there is an aortic diastolic murmur with the usual circulatory dynamics accompanying aortic insufficiency. In cases of rupture of the mitral valve or chordae there is a loud, systolic murmur, maximal at the apex and left sternal border, usually accompanied by a thrill and occasionally accompanied by an apical diastolic murmur. Cardiac enlargement and congestive heart failure usually develop gradually after many months. Rupture of a papillary muscle may give similar signs, but there is likely to be a rapid development of acute left heart failure and death within hours or days. Recent previous cardiac examination wtih negative findings is an important and often the decisive clue to diagnosis.

Superficial *pericarditis* may be disclosed by the presence of a friction rub or there may be associated physical, roentgenologic and electrocardiographic signs of pericardial effusion. With rupture of the heart there is likely to be a hemopericardium which causes cardiac tamponade.[17] Extensive hemothorax is commonly associated due to rupture into the pleural cavity.

Electrocardiographic changes may result from pericarditis or hemopericardium, from direct myocardial injury or from myocardial necrosis secondary to thrombosis of a coronary artery. In cases of pericarditis caused by nonpenetrating chest injuries, Wood[98] described electrocardiographic abnormalities similar to, though often distinguishable from those characterizing myocardial infarction. He emphasized that in cases of cardiac contusion T wave inversion and ST deviations were most striking in lead II while in cardiac infarction discordant ST and T wave changes were most apparent in leads I and III. Burstein and Marshak[18] reported two cases of cardiac contusion with electrocardiographic findings of T wave depression or inversions, in one of which these abnormalities alone permitted the diagnosis. The precordial lead disclosed the earliest and most constant findings.

Numerous reports of cardiac injury by penetrating or nonpenetrating trauma have confirmed the occurrence of ST elevations or depressions or T wave inversions, but no uniform pattern has been described. Apparently the site and extent of the lesion and the interval between the injury and electrocardiographic examination account for the described variations. As a rule ST and T wave changes are transient and disappear within a few weeks and almost always within three months. In addition to the above the electrocardiograph may disclose transient or persistent auricular fibrillation, heart block or bundle branch block.

Diagnosis

The diagnosis of cardiac contusion must be entertained whenever an individual experiences a blunt injury of the chest wall. In general, the greater the momentum of the blow and the greater the proximity to the precordium, the

more likely the cardiac injury. Occasionally cardiac contusion or rupture follows extreme compression of the abdomen or thighs.[53]

Serial electrocardiograms should be taken in all cases of chest trauma. Depressed or inverted T waves, auricular fibrillation or heart block may suggest cardiac injury whether clinical symptoms and signs are present or not. Roentgenologic films of the chest should be made to study the size, form and pulsations of the cardiac silhouette. Such study may determine the presence of pericardial effusion and serves also to exclude pulmonary lesions as the possible cause of the patient's symptoms.

Pericardial paracentesis should be performed if there are physical or roentgenologic signs of pericardial effusion or if there are symptoms and signs of acute cardiac tamponade. If there are symptoms and signs of acute circulatory failure the findings should be reviewed to determine the presence of cardiac compression. Hemopericardium following a nonpenetrating chest injury suggests cardiac contusion and perforation of a chamber or laceration of a coronary artery.

The diagnosis of cardiac damage due to nonpenetrating trauma should also be considered if a pericardial friction rub appears soon after the injury, if loud murmurs or thrills develop, or if clinical or electrocardiographic signs of cardiac anoxia or cardiac infarction appear.

The presence or absence of preexisting disease is often of primary importance in the interpretation of post-traumatic symptoms and signs. Since cardiac trauma is often likely to involve insurance, workmen's compensation or liability problems, careful cardiac examination when insurance is first granted and when the patient is first seen after an accident are essential.

Prognosis

There are inadequate data for definitive statements as to prognosis. Rapid fatalities follow rupture of the heart either immediately after the injury or a week or two later. Less serious but severe injury may be complicated by heart failure, angina pectoris or evidence of myocardial infarction. The outlook is then similar to that in cases due to nontraumatic causes. Rupture of a valve is usually followed by fatal heart failure within a year or two. Arrhythmias such as paroxysmal tachycardia, auricular fibrillation and heart block usually disappear within a few days or weeks but may be prolonged and may be complicated by heart failure. Greater recognition of the frequency of cardiac contusion and more careful diagnostic methods are leading to discovery of the mild cases in which recovery is the rule.[2]

Treatment

In cases with very severe injuries and rupture of the heart death often occurs too rapidly to permit surgical treatment. But when a sufficient interval elapses and there are signs of increasing cardiac compression, pericardial aspiration should be performed. If hemopericardium is proved and no relief is obtained or if following aspiration there is only transient improvement with recurrent relapse, surgical exploration of the heart should be undertaken. If a cardiac rupture is discovered, it should be sutured as noted above (p. 983) or a pericardial graft can be sutured over a softened area. The use of the newer blood products and absorbable gelatin or cellulose preparations[49] may be valuable to control bleeding of softened areas, as in rupture of the liver.

In patients with symptoms such as weakness, arrhythmia, angina pectoris

or heart failure, or in patients with significant electrocardiographic changes, sharp restriction of activity or limited confinement to bed for three to six weeks or longer may be necessary to avoid rupture of a lacerated myocardium. The usual measures designed to control heart failure or cardiac pain should also be instituted.

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CARDIAC TUMORS

Tumors of the heart and pericardium have evoked an extensive literature out of all proportion to their uncommon incidence and their relative unimportance as a cause of clinical heart disease. This unusual interest has been aroused by four aspects of the subject:

(1) Uncertainty as to the nature and pathogenesis of cardiac myxoma and rhabdomyoma.

(2) The occurrence of clinical features which may simulate those of common forms of heart disease.

(3) The ability to diagnose cardiac tumors during life.

(4) The possibility of surgical removal and cure of certain cardiac tumors.

INCIDENCE

Reviews of the literature have been composed by Pearlstein[48]; Mandelstamm[40]; Yater[84]; Strouse[70]; Lisa et al.[35]; and more recently by Mahaim,[39] who devoted a large volume exclusively to cardiac tumors. Mahaim believes that the incidence of cardiac tumors has been underestimated. Lymburner[38] encountered only 4 primary tumors of the heart (0.05 per cent) and 52 secondary tumors (0.6 per cent) in a series of 8500 autopsies at the Mayo Clinic. Similarly Pollia and Gogol[50] discovered only 29 secondary tumors (0.25 per cent) in 12,000 autopsies and Scott and Garvin[60] 118 metastatic neoplasms of the heart and pericardium (1.0 per cent) in a series of 11,100 postmortem examinations. Malignant neoplasms of the heart and pericardium compose 6 to 11 per cent of malignant tumors of all kinds throughout the body.[79, 60]

CLASSIFICATION

Cardiac tumors may be classified as follows:

(I) Primary tumors of the heart
  (A) Benign
    (1) Myxoma
    (2) Rhabdomyoma
    (3) Other rarer tumors
      Fibroma, lipoma, angioma, papilloma, teratoma, leiomyoma, xanthoma
  (B) Malignant
    (1) Sarcoma—various types

(2) Other rarer malignant tumors
Mesothelioma or mesothelial sarcoma of the pericardium, rhabdomyosarcoma, epicardial epitheliomas.

(II) Secondary (malignant) tumors
(A) Carcinoma and occasional sarcoma by direct invasion
(B) Carcinoma or sarcoma by metastasis
(C) Systemic neoplastic disease with cardiac involvement
(1) Hodgkin's disease
(2) Lymphosarcoma
(3) Leukemia
(4) Kaposi's sarcoma
(5) Neurofibromatosis (von Recklinghausen's disease)

PATHOLOGY

Primary Tumors

These are extreme rarities. Altogether Lymburner[38] was able to collect 226 instances of primary cardiac tumors from the literature. Of the primary tumors, the benign occur more often than the malignant. Myxoma, sarcoma and rhabdomyoma are the commonest primary tumors in the given order of frequency. The myxoma, the polypoid fibroma and sarcoma arise from the endocardium. Rhabdomyoma and fibroma arise from the myocardium while mesothelioma or mesothelial sarcoma, lipoma, fibroma, angioma are among the tumors of pericardial origin.

Benign Primary Tumors. *Myxoma.* The myxoma is a solitary globular or polypoid tumor varying in size from that of a cherry to a large peach. It is semi-translucent, yellowish-gray in appearance and elastic and gelatinous in consistency. Its cut surface is mucinous or gelatinous and may be more or less hemorrhagic. The myxoma occurs chiefly in the left atrium, arising usually from the atrial septum near the rim of the fossa ovalis, to which it is attached by a short stalk. From this pedicle the myxoma extends to fill some or most of the atrial cavity and may even occlude the mitral orifice and produce all the disturbances of a mitral stenosis. The myxoma may also arise near the margin of the left auricular appendage or less often from the right atrium or ventricles. A myxoma of the left ventricle with occlusion of the abdominal aorta and renal arteries by tumor embolus was reported by Young and Hunter.[85]

Microscopically the myxoma is seen to be composed of an amorphous or mucoid matrix with characteristic stellate or spindle-shaped cells, acini of large polyhedral cells, delicate scanty blood vessels, occasional lymphocytes and plasma cells, small hemorrhages or blood pigments (hemosiderin or hematoidin) and very small amounts of collagenous and elastic fibers. Variations in the appearance and predominance of these individual microscopic elements of myxoma account for other names applied to this tumor, e.g., hemangio- or fibro-myxoelastoma,[9] lymphangioendothelioma,[36] fibromyxoma, fibroma, hemangiomyxoma.

The weight of evidence appears to favor the concept that the myxoma is a true neoplasm,[84, 16] as maintained by Ribbert.[54] The neoplasm may arise in rests of embryonic mucoid tissue or it may represent an endothelioma with myxomatous degeneration.[45] However, following the interpretation of

Thorel,[73] many writers view the myxoma as a thrombus which has swollen by imbibition and undergone organization.[24, 41] In the case reported by Dexter and Work,[13] the authors suggested that rheumatic inflammation of the left auricle predisposed to the formation of the myxoma, but rheumatic lesions have not been reported in other cases of myxoma.

Myxomata of the cardiac valves have been described as distinctive shaggy tumor masses, which are probably true tumors but have also been interpreted as exaggerated Lamblian excrescences. Fibroma of the valves has been described.[71] This occurs as a solitary round or oval, broad or pedunculated solid tumor with a slight predilection for the tricuspid valve. It is probably a true tumor arising from the valvular subendothelium but it has also been interpreted as an organized thrombus.

Rhabdomyoma. The rhabdomyoma is a congenital glycogen-containing tumor which occurs as multiple or solitary nodules or as a diffuse infiltration of the myocardium.[15, 6] Most frequently there are multiple gray or purplish nodules lying within the myocardium, bulging externally on the epicardial surface, or projecting into the lumen of the cardiac chambers. They occur oftenest in the left ventricle but may affect any portion of the heart including the valvular leaflets. Less often there are solitary nodules which are usually located in the region of the apex. Occasionally there is diffuse cardiac involvement and enlargement without distinctive tumor formation; this type of case may be a form of von Gierke's glycogen storage disease.[32]

According to Batchelor and Maun,[6] 63 authentic cases of congenital glycogen tumors had been described since the first case reported by von Recklinghausen[53] in 1862. In most instances death occurs in the first year of life, and in 86 per cent before puberty. A striking feature is the usual association of multiple cardiac rhabdomyoma with tuberous sclerosis of the brain, multiple tumors of the kidney and adenoma sebaceum of the skin.[66] The solitary cardiac rhabdomyoma is not accompanied by such lesions. This combination of tumor-like deformities in several organs simultaneously has cast doubt on the concept of Wolbach[82] and others that rhabdomyoma is a true tumor of embryonal cardiac muscle cells. Instead, the teratogenetic character of the tumor-like lesions suggests that they represent simultaneous tissue malformations in the various organs. The term hamartoma[2] has been applied to these tumor-like formations caused by errors in tissue development.[59] Occasionally fibrosis and calcification occur in a rhabdomyoma, features which have led Olsen and Cooper[44] to interpret the nodules as resulting from congenital glycogenic degeneration of the myocardium.

Microscopic examination of cardiac rhabdomyoma discloses a spongy tissue containing many large stellate cells which form peculiar vacuolated structures. These vacuoles lie within the cell body of large embryonic-like muscle fibers[61] and contain glycogen as may be demonstrated by Best's carmine stain.[1]

Other benign primary tumors have been described in solitary case reports. *Fibroma* of the valves has been mentioned. Fibroma may also occur as a solid gray or white polypoid tumor of the left or right atrium or as a more or less circumscribed mass within the myocardium of the ventricles or ventricular septum. *Lipoma or fibrolipoma* occurs occasionally as a single tumor of great size or in the form of multiple fatty tumors. Cases of lymphangioendothelioma reported by Armstrong and Mönckeberg[3] and by Lloyd[36] are of special interest

because they involved the auriculoventricular node and caused heart block. Teratoma arising in the mediastinum may rarely involve the pericardium[27, 80] and cause symptoms of acute or chronic cardiac compression, or may become infected and produce symptoms of purulent pericarditis.[7]

Malignant Primary Tumors. *Primary Sarcoma.* Sarcoma of the heart is the almost exclusive representative of primary malignancy of this organ. Many varieties have been described including fibrosarcoma, spindle cell sarcoma, round cell, giant cell, myxosarcoma, rhabdomyosarcoma[34] and mesothelioma (mesothelial sarcoma, endothelial sarcoma). Kaposi's sarcoma of the heart[77] has sometimes been reported under the heading of angiosarcoma,[76] angioendothelioma[22] and angioreticuloendothelioma.[11] The sarcoma may arise from the endocardium or pericardium or more rarely from the myocardial layer (rhabdomyosarcoma).

According to Weir and Jones,[76] 76 cases of primary sarcoma of the heart and pericardium had been reported. In about 50 per cent of the cases in which the site was mentioned, the malignant tumor arose from the right atrium. This contrasts with the commonest benign tumor (myxoma) which arises usually from the left atrium. Primary sarcoma may also originate in the pericardium,[67] but only 22 cases had been reported up to 1947.[52] Isolated instances of sarcoma of the left atrium[29] or other portions of the heart have also been noted. Mahaim[39] has described cases of mesothelioma arising from epicardial inclusions in the septum near the a-v node.

The primary cardiac sarcoma metastasizes most commonly to the pleura and lung but also to the mediastinal tracheobronchial or retroperitoneal lymph nodes, to the adrenals, to other parts of the heart or to the brain. Haythorn et al.[26] described a case of primary fibromyxosarcoma of the heart and pulmonary artery with extensive metastasis along the pulmonary arterial tree, bronchi and lungs. The roentgenologic appearance resembled that of carcinoma or Hodgkin's disease of the lungs.

The primary sarcoma arising from the right atrium is usually a large firm gray or yellowish papillary tumor which may fill most of the atrial cavity; it may extend toward the right ventricle to occlude the tricuspid orifice or it may invade or occlude the venae cavae.

Pericardial sarcoma forms a more diffuse white or yellowish tumor mass, often of massive thickness (1 to 5 cm.) and extent, which deforms or obliterates the cardiac contours, and partially or completely glues the pericardial layers.[67, 46] The tumor itself reveals many areas of hemorrhage and necrosis. It may be confined entirely to the pericardium, it may compress the myocardium from without or it may actually invade the heart muscle and replace more or less extensive portions. The base of the pulmonary artery and aorta may be incorporated in the dense tumor mass and rendered relatively fixed. The pericardial cavity often contains a serofibrinous or serohemorrhagic effusion which occasionally becomes infected. Pleural effusions, sometimes bloody, may be associated, either due to direct neoplastic invasion of the pleura or secondary to cardiac compression and heart failure.

Secondary (Metastatic) Cardiac Neoplasms

Secondary tumors occur with much greater frequency than primary tumors of the heart. Most of the secondary tumors are carcinomata but metastatic

sarcomata also occur. Carcinoma usually appears as single or multiple, discrete small white firm nodules, but it may occur as a more diffuse infiltration. Carcinoma of the heart may also present as miliary infarction without gross metastases. Carcinomatous emboli may be observed in branches of the coronary arteries. A carcinomatous lymphangitis may occur. Sarcoma occurs chiefly as diffuse infiltrating masses in the pericardium and myocardium. They may broaden the cardiac walls and may encroach on the cardiac cavities or protrude externally. Like primary sarcoma, secondary sarcoma of the pericardium may produce massive thickening of the pericardium, a serofibrinous or fibrinopurulent effusion, which is often hemorrhagic, or a completely adherent pericardium.

Metastatic neoplasms may invade any part of the heart including the pericardium, the ventricles, atria, ventricular septum and occasionally the conduction system.[39] The endocardium and valves are very rarely involved, but I have seen carcinomatous implants on the mitral valve secondary to a carcinoma of the uterus, and on the tricuspid valve secondary to carcinoma of the gallbladder. In general the right side is involved more often than the left side of the heart.

Most of the secondary cardiac neoplasms have their primary origin in malignant tumors of the bronchi, lungs and breast.[60, 42] But the primary neoplasm may be situated in the esophagus, mediastinum, thyroid, uterus, genitourinary tract and many other organs.[55] Melanosarcoma and carcinoma of the skin not infrequently metastasize to the heart.[43, 12] I have observed a case of Ewing's sarcoma of bone which had given rise to a cherry-sized polypoid metastasis of the left ventricle near the apex.

Invasion of the heart by secondary tumors most often occurs by direct extension from neighboring intrathoracic organs (chiefly bronchi, lungs, pleura, thymus, mediastinal glands and tissues). The malignant tissue infiltrates the pericardium and may also invade and replace the myocardium. Intrathoracic neoplasms may also break into a pulmonary vein, and by passage through the left atrium, left ventricle, aorta and coronary arteries reach the cardiac tissues. Direct invasion of the heart may result from extension of tumor masses through the inferior vena cava to the right atrium. This may be the mechanism in cases of renal hypernephroma and in occasional instances of testicular teratoma, hepatic malignancies and chondrosarcoma. Less often cardiac metastases are secondary to malignant tumors in distant organs. The malignant cells reach the heart by passage through the blood stream. Tumor cells have actually been found in the circulating blood and endocardial vegetations. Least commonly, secondary neoplasms of the heart result from retrograde lymphatic extension from neighboring intrathoracic organs or lymph nodes.

A variety of systemic neoplastic diseases rarely involve the heart; in these instances the pericardium is usually involved. The most common of these are Hodgkin's disease,[25, 56] lymphosarcoma[68] and reticulum cell sarcoma.[23] Invasion of the heart usually follows direct extension or retrograde lymphatic spread from involved mediastinal lymph nodes. I have also observed a thymic lymphosarcoma which infiltrated the parietal and visceral pericardium. Like other pericardial sarcomata, the lymphomatous lesions of the pericardium are often associated with pericardial effusions which may be hemorrhagic.

Occasionally leukemic infiltrations are found in the pericardium or myocardium. Kaposi's sarcoma involving the heart[77] and neurofibromatosis with cardiac involvement have also been reported.

CLINICAL MANIFESTATIONS OF CARDIAC TUMORS

Most cardiac tumors produce no clinical symptoms and are discovered only at postmortem examination. In some cases of secondary cardiac tumors, the symptoms referable to the cardiac metastases are obscured or overshadowed by those of the primary disease. Occasionally, however, both primary and secondary tumors give rise to distinctive clinical features which permit an accurate diagnosis. In the latter group, symptoms are dependent on the location and to some extent on the size of the tumor. Symptoms result from interference with the passage of blood through the heart, impaired transmission of the cardiac impulse through the conduction system, pericardial reaction or rarely from extensive myocardial damage. Somewhat characteristic clinical syndromes may be associated with a few of the individual cardiac tumors.

Congestive Heart Failure. Symptoms of congestive heart failure are generally regarded as the most common manifestations of cardiac neoplasms. These include dyspnea and orthopnea and venous engorgement, with or without peripheral edema and serous effusions. Careful analysis discloses that these symptoms do not usually represent heart failure caused by extensive neoplastic myocardial damage. In some instances the dyspnea results from the primary pulmonary neoplasm, while the venous engorgement is the consequence of metastatic involvement of lymph nodes and mediastinal tissues with obstruction of the superior vena cava. In others, symptoms indistinguishable from heart failure are due to subacute or chronic cardiac compression (tamponade) by extensive malignant pericardial involvement with or without effusion. But typical manifestations of congestive heart failure may be caused by longstanding functional mitral stenosis due to a myxoma or other polypoid tumor of the left atrium which occludes the mitral orifice. Progressive heart failure and sudden death in a case of myxoma of the left atrium have been attributed to pressure on the pulmonary veins.[72] Only occasionally is heart failure produced by extensive sarcomatous destruction of the myocardium. The heart failure due to cardiac tumors is characterized by its intractable, rapidly progressive course and its failure to respond to all therapy. Its sudden and unexplained development has also been remarked.

Chronic cardiac tamponade and superior caval syndrome result from lymphomatous, metastatic or primary malignant neoplasms of the pericardium. In some of these cases the onset with cough, malaise and fever suggests a diagnosis of "grippe." Later the full clinical picture develops with increasing dyspnea, engorgement of the cervical veins, enlargement of the liver and small rapid pulse.

Weller[77] associated Kaposi's sarcoma of the right atrium with a distinctive syndrome which, he believed, permitted clinical recognition. The onset resembled that of an acute upper respiratory disease which became protracted (cough, malaise, weakness, night sweats and occasional hemoptysis). Edema of the face, at first transitory, was later striking and permanent. Other features were cyanosis, fever between 100° F. and 101° F., and roentgen ray shadow of a mass along the right atrial border, with or without evidence of pericardial

effusion. However, these symptoms and signs are not specific and may be encountered with any malignant tumor of the right atrium and with pericardial malignancies which eventually obstruct the superior vena cava.

Acute circulatory failure with a shock-like syndrome is apt to result from a ball-valve tumor of the left atrium, which intermittently and increasingly obstructs the mitral valve.[47, 31] Transient obstruction of the circulation, sometimes associated with change of position in bed, may cause attacks of faintness or syncope, cold extremities and cyanosis.[53a] Peripheral cyanosis, localized necrosis of the tip of the nose, fingertips and toes, or gangrene may result from prolonged intense circulatory obstruction.

A huge ball-valve thrombus of the *right* atrium in a patient with mitral stenosis and auricular fibrillation was reported to produce: dusky cyanosis of the face and neck, engorgement and systolic pulsation of the cervical veins, enlargement and systolic pulsation of the liver, air hunger without pulmonary congestion, pronounced enlargement of the right heart, especially the right atrium, and rapid variations in the severity of the clinical features.[83]

Acute malignant pericarditis or pericarditis with effusion may be evidenced by a friction rub over the precordium or by physical and roentgenologic signs of diffuse, water-bottle type of cardiac enlargement. In several cases of malignant pericarditis that I have observed, a pericardial rub persisted for more than thirty days. Symptoms and signs of cardiac tamponade may develop rapidly only after many months. Pericardial aspiration may yield a serofibrinous exudate or a serosanguineous effusion, but a "dry tap" may be encountered because of complete pericardial adhesion. When pericardial effusions due to malignancy are aspirated, there is a tendency to rapid refilling of the sac. Pleural effusions, also frequently hemorrhagic, are likely to accompany pericardial effusions because of direct extension of the malignancy to the pleura.

Arrhythmias are relatively common. The most characteristic are auricular fibrillation and flutter, which may appear as transient paroxysms but later persist.[18, 4] Paroxysmal tachycardia, frequent premature beats and occasionally heart block or bundle branch block have also been reported. The arrhythmias are usually encountered in cases with metastatic neoplasms of the atria, especially the right atrium. Heart block has been associated with lymphangioendothelioma[3, 36] and hemangioendothelioma[21] of the auriculoventricular node and with multiple rhabdomyomata. Perry and Rogers[49] reported a case of Adams-Stokes syndrome with heart block, due to cardiac lymphangioendothelioma.

Signs of valvular disease, usually those of mitral stenosis[37, 17] and occasionally of tricuspid stenosis,[78, 69] may be present in cases of polypoid tumor of the atria. Myxoma of the left atrium is the commonest cause of this form of functional valvular stenosis but less commonly a pedunculated sarcoma[29] or metastatic sarcoma is responsible. In 1933 Ludwig[37] assembled 21 cases including one of his own, in which tumors of the left atrium had caused a functional mitral stenosis. Wainwright[74] reported a case of metastatic sarcoma which reached the left atrium and mitral valve and produced signs of mitral valvular disease.

The murmurs may be typical of mitral (or of tricuspid) stenosis or they may be bizarre in quality, location and variability. Occasionally in cases of ball-valve neoplasms, the murmur varies or disappears with change in the patient's position.

Sudden death is relatively frequent, especially in primary tumors of the heart. This was the mode of exitus in one third of the cases of myxoma or fibroma of the atria and in about three quarters of the rare cases of lymphangioendothelioma. It is also common with cardiac rhabdomyomata. Sudden death may follow a period of intermittent or persistent circulatory failure, but it also occurs without preliminary circulatory symptoms.

A variety of other clinical manifestations may owe their genesis to cardiac tumors. *Angina pectoris* and typical manifestations of *coronary artery occlusion* may result from neoplastic involvement or obstruction of the coronary vessels. In one of Fishberg's[18] cases, continuous cardiac pain for sixteen days was due to a tumor encircling the left circumflex artery. Nonspecific chest pain occurs in cases of pericardial neoplasm. Primary or secondary pericardial sarcoma may cause rapid death by rupturing into the pleural cavity. I have seen a perforation of the inferior vena cava by a mediastinal chorioepithelioma. I have also observed the clinical picture of Laennec's cirrhosis with ascites, edema of the lower extremities and dilatation of the veins of the abdominal wall, caused by an adenoma of the left kidney which extended into the inferior vena cava and up to the right atrium. Postmortem examination revealed also an adherent fibrous pericardium and thrombosis of the hepatic veins. Rarely a myxoma of the left atrium causes embolization and infarction of various organs.[10] Convulsions in cases of cardiac tumor may be due to heart block (Adams-Stokes syndrome) or to tuberous sclerosis of the brain associated with cardiac rhabdomyomata. *Congenital rhabdomyomata* may produce cardiac murmurs when the tumors are situated on the valvular leaflets, and arrhythmias are not uncommon due to atrial involvement.[75] In addition these cases are characterized by cyanosis at birth and indifference to surroundings; later there is delay in walking and in mental development, epileptiform seizures and sudden death during an apparently minor ailment.

Roentgenologic examination may disclose bizarre, irregular protuberances or advanced universal enlargement of the cardiac silhouette with obliteration of the normal cardiac curves. The appearance may resemble that of a pericardial effusion or localized bulges may simulate ventricular aneurysm or pericardial cyst.[30, 19] Polypoid tumors of the left atrium may effect "mitralization" of the cardiac shadow with straightening of the left border and prominence of the left pulmonary salient.

The *electrocardiogram* is not usually distinctive.[64] It may depict auricular fibrillation or flutter due to atrial involvement,[18] or rarely heart block[36, 38] or bundle branch block[81] and P wave abnormalities in atrial neoplasms.[70] Elevation of the RS-T segments and inversion of T waves in leads I and II were documented by Boman[8] in a case of primary sarcoma of the pericardium. In a case of carcinoma of the esophagus with massive metastases and extensive destruction of the heart muscle, Rosenbaum[57] et al. observed persistent upward displacements of the RS-T segments in leads II, III, V_F and in unipolar leads. They interpreted these findings, which resembled those seen following combined anterior and posterior infarction, as being due to continuous acute myocardial injury by invading neoplasm. Although the electrocardiogram in occasional cases of cardiac neoplasm has been mistaken for that of anterior or posterior wall infarction, the characteristic discordant ST elevation and depression of the latter in leads I and III have not been described.

DIAGNOSIS

More than twenty reports have been made of correct antemortem diagnosis, most of them in recent years and usually in cases of secondary (malignant) tumors of the heart.[81, 18, 58, 65, 14] Primary tumors have also been recognized during life by Barnes et al;[5] Popp;[51] Shelburne;[62] Lange and Christiansen.[33] Because of the possibility of surgical removal, the recognition of benign tumors is especially important.

As with other rare forms of heart disease, diagnosis depends on alert awareness that cardiac neoplasm may be responsible for cardiac manifestations, especially when the clinical course is atypical. In the presence of a malignant neoplasm elsewhere in the body, especially in the neighboring thoracic organs, certain clinical features should suggest the occurrence of cardiac metastases. These diagnostic features are:

(1) The rapid onset of congestive heart failure without apparent cause and its unabated progression despite treatment.

(2) The development of signs of fibrinous pericarditis or pericarditis without other apparent cause. The pericardial rub, if present, persists for many days or weeks. A blood-tinged pericardial tap is confirmatory[62] and the finding of tumor cells is diagnostic.[28, 58, 63]

(3) The occurrence of paroxysmal or persistent auricular fibrillation or of heart block in the absence of the usual causes of these disturbances.

(4) The development of cardiac tamponade as indicated by dyspnea, engorged veins, hepatic enlargement, falling blood pressure and pulse pressure, tachycardia and pulsus paradoxicus.

The *diagnosis of primary tumors* is more difficult. Signs of mitral stenosis in the absence of a history of rheumatic fever, together with symptoms and signs of ball-valve obstruction of the mitral valve (p. 576), should suggest the possibility of a polypoid myxoma, fibroma or sarcoma of the left atrium. Similarly the presence of right atrial tumor may be suggested by a tricuspid murmur, congestive right-sided heart failure without apparent cardiac or pulmonary disease, or evidence of superior vena caval obstruction (edema and cyanosis of the neck and face and venous engorgement with or without dilated collateral veins on the chest wall).

Primary tumors of the pericardium (teratoma, sarcoma) may be recognized by physical signs of pericarditis or pericardial effusion or by bizarre, localized bulges of the roentgenological silhouette of the heart. Angiocardiography, fluoroscopy and kymography may differentiate these tumors from aneurysms, since the tumors do not fill with diodrast and pulsation is absent or only transmitted; the latter is not an absolute distinction. *Rhabdomyoma* may be suggested by the association of cardiac enlargement, cardiac irregularity, and convulsive seizures with or without Adams-Stokes syndrome in backward, mentally deficient infants or children, who may have adenoma sebaceum.

TREATMENT

Treatment of the secondary neoplasms of the heart is merely symptomatic, as the ultimate fate is hopeless. Acute cardiac tamponade due to rapidly accumulating pericardial effusion may require frequent paracentesis of the pericardium. Rapid relief of alarming circulatory deficiency followed the

aspiration once of 340 cc. and again of 300 cc. of extremely hemorrhagic fluid in a case of metastatic carcinoma of the pericardium reported by Barnes, Beaver and Snell.[5] Deep roentgen ray therapy may temporarily destroy pericardial neoplasms or lymphomata and effect more or less symptomatic relief as in the case of pericardial metastasis reported by Shelburne and Aronson,[63] and as in the case of Hodgkin's disease of the pericardium reported by Garvin.[20] Nitrogen mustard, radioactive P^{32} or urethane therapy may be tried.

Hope for surgical removal of primary tumors was engendered by Beck's[7] report of a case of an intrapericardial teratoma and one of tumor of the heart in which the lesions were successfully extirpated and the patients cured. Further efforts of this type are dependent on accurate clinical diagnosis.

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FUNCTIONAL MANIFESTATIONS REFERRED TO THE HEART

The physician is confronted more often with functional disturbances which the patient refers to his heart than with organic cardiac abnormalities.[1, 14] Proper treatment requires the ability not only to differentiate these functional disorders from organic heart disease but also to recognize them when superimposed on organic heart disease. These functional problems will be discussed under the following headings:

1. "Neurocirculatory asthenia" or "cardiac neurosis."
2. Isolated and transient functional cardiac symptoms.
3. Objective functional cardiac signs.
4. Phobias of heart disease.
5. Fainting or syncope.

"NEUROCIRCULATORY ASTHENIA" OR "CARDIAC NEUROSIS"

Definition

"Neurocirculatory asthenia" (NCA) refers to an ill defined syndrome of psychogenic or neurogenic origin, often mistaken for organic heart disease and characterized by dyspnea, precordial pain, palpitation, exhaustion and a general incapacity or inefficiency in adjusting to physical or emotional strain.

Despite the distinctive titles given to this syndrome it is not a nosological entity. It is nothing more than a moiety of the more general picture of psychoneurosis, which, in the cases under discussion, chances to assume entirely or predominantly the garb of cardiac or circulatory symptoms.[38] Hence the term "cardiac neurosis." DaCosta[7] in 1871 applied the title "irritable heart," but recognized that the manifestations were due to a functional cardiac disorder. "Disordered action of the heart" (DAH) and "soldiers' heart"[25] were popular terms during World War I. Parkinson[32] and Lewis[23] employed the synonym "effort syndrome," because the symptoms were readily induced by minor exertion. Oppenheimer and associates[30] first employed the label "neurocirculatory asthenia" to denote a generalized weakness of the circulatory system, due more particularly to its innervation, but they clearly recognized the importance of the psychoneurotic factor in its causation.

Etiology and Pathogenesis

Underlying Cause. Psychologic Disturbances. The underlying cause appears to be a fundamental ego insecurity arising from psychologic problems which began in infancy and childhood. In the vast majority of cases, a careful history discloses previous serious maladjustments or "nervous breakdowns," long absences from school or work, or unexplained prolonged illnesses.[31, 42, 19]

That psychologic disturbances frequently present their somatic extension into the cardiac sphere is not surprising. The heart is the traditional center of emotional expression. There is an early awareness of changes in cardiac activity with the strain of physical and emotional activities.[2] Literally and figuratively life and its emotions are symbolized in the beat of the heart and death in its stoppage. Death fears and death wishes are psychologically interwoven in the maladjusted person and the heart is an appropriate site for their somatic expression. Finally, accidental factors often determine the cardiac localization of psychoneurotic disturbances, e. g., the inadvertent remark of a physician, rejection of an application for life insurance, news of cardiac disease or of the cardiac death of a relative, friend, neighbor or prominent person, or the experience of palpitation or precordial discomfort.

Physiologic Mechanism. In recent years physiological methods have been applied to the study of functional disorders of the heart and an effort has been made to interpret these disorders in terms of pathologic physiology. The similarity of the manifestations of neurocirculatory asthenia to those associated with stimulation or inhibition of the sympathetic and vagal nervous system suggested that the syndrome was due to "autonomic imbalance."[22] On the basis of clinical and experimental data a more primary origin of the "autonomic imbalance" is postulated in the hypothalamic region and the latter is conceived as being functionally disturbed by abnormalities in cortico-hypothalamic control.[14] Since the hypothalamus is a center for the mediation of numerous endocrine and metabolic as well as autonomic nervous functions, the concept of an hypothalamic origin of neurocirculatory asthenia is at best a nonspecific one. A hypothalamic disturbance can be assumed with equal propriety for gastrointestinal and other visceral functional disturbances as well as for a host of so-called psychosomatic diseases.

NCA and Hyperventilation. The similarity of certain symptoms of NCA to those of hyperventilation[21] suggested that the latter was a major factor in the production of functional cardiac manifestations.[35] However, it has been amply demonstrated that these symptoms usually appear in the absence of hyperventilation and the latter is merely one, and only an occasional one of the manifestations of the underlying psychologic or neural disturbance.[17, 44]

NCA and Graves' Disease. Because of a resemblance of functional cardiac symptoms to some of the symptoms of hyperthyroidism, NCA has been interpreted as an earlier and larval form of Graves' disease.[27, 28] This relationship has not been demonstrated for any significant number of cases.

Extrinsic Factors—Relation of War and Strain. Neurocirculatory asthenia is predominantly a disorder of civil life, but it appears in a more striking form and has been studied most extensively among soldiers during war. As in previous wars the outbreak of World War II was soon followed by the publication of numerous studies of NCA.[23, 36, 10, 42, 20] I have indicated that the fundamental cause of NCA is a psychologic insecurity and maladjustment,

but the onset of overt symptoms, as with all psychoneurosis, is usually precipitated by some extrinsic environmental strain. War presents a particularly intense life strain with removal from family and friends, dislocation of environment and activity, new competitive situations, close exposure to severe physical exertion, intense anxiety and fear as well as risk of death. In civilian life the symptoms of neurocirculatory asthenia are likewise precipitated by stress-producing life situations associated with fear, anxiety, anger, frustration and despair.[43] However, these are rarely as intense as those presented by intimate and prolonged exposure to the actual hazards of war. The more serious the intrinsic psychiatric difficulty, the less severe is the external factor needed to precipitate symptoms. Conversely even the so-called normal individual may exhibit functional cardiovascular symptoms if the environmental strain is extremely intense and prolonged.

Age. In its overt form neurocirculatory asthenia is said to occur most commonly between the ages of twenty to forty but this is largely a matter of terminology. It may occur at any age.

Sex. In civilian life it is more more common among females than among males. This is probably due to the relatively greater ego security which our civilization affords to the male.

Heredity. Functional cardiovascular or other psychoneurotic symptoms are common among the parents and siblings of patients with neurocirculatory asthenia. It is probable that similar environmental factors and the parental imposition of similar neurotic standards of behavior are more important than the inheritance of nervous or circulatory inferiorities by way of the germ plasm.

Infections. Acute infections have often been arraigned as precipitating causes of NCA. While this relationship is possible, not only physical factors but complex psychologic ones may be involved. Sometimes maternal or familial overprotection and overanxiety during a childhood illness set up a pleasant subconscious association with ego importance and exaggerated parental attention. Often this initiates abnormal anxieties regarding illness and a withdrawal from physical exercise, especially active sports. With subsequent illnesses the pattern both of anxiety and prolongation of disability tends to recur.

Symptoms

Dyspnea is usually the commonest and most distressing symptom. It generally occurs at rest and is described as an inability to take a deep breath and not as a panting such as follows exertion. There is often an irregular sighing which is readily demonstrable in the curve of a basal metabolism test. The incidence and severity of the dyspnea are disproportionate to the degree of exercise and to the objective disturbances in ventilation.[5]

There are occasionally spontaneous attacks of dyspnea and tachypnea which have been described as the hyperventilation syndrome. They have been interpreted as a psychogenic expression of the fear of suffocation, especially in patients with claustrophobia.[42] These outbursts are often associated with tachycardia, giddiness, axillary and palmar sweating, and anxiety and may culminate in frank tetany.[9] Patients with NCA and respiratory symptoms exhibit a diminished capacity for breathholding.[40, 44]

Pain in the precordium is usually distinctive from that of angina pectoris.

It may be a dull, continuous ache or soreness or may be sharp, intermittent and dartlike. The pain is usually localized to the region of the apex of the heart, the nipple or inframammary area. It is either unrelated to effort or occurs some time *after* a tiring exertion. Unlike the pain of angina pectoris it does not compel the patient to stop activity nor is it rapidly relieved by rest. Occasionally there is an associated local precordial tenderness which may be abolished by the infiltration of procaine.[34] The precordial pain of NCA has been attributed to excessive use and tonic spasm of the intercostal muscles.[44] This explanation is based on the observation that patients with functional cardiovascular disturbances tend to breathe almost exclusively with their chest wall and not with their diaphragm.[44, 12]

Palpitation occurs commonly. As the rule there is an uncomfortable awareness of the heart beat in the absence of any arrhythmia. But tachycardia and a forceful cardiac pulsation are often present. Occasionally premature beats or paroxysmal tachycardias account for distressing cardiac discomfort, pain and intense anxiety.

Fatigability is a characteristic feature of neurocirculatory asthenia. It takes two forms: One is a sense of great fatigue on arising in the morning, which gradually diminishes in the course of the day's activity. The other is a profound exhaustion following relatively minor physical exertion. In severe cases of NCA the patient spends many hours in bed during the day as well as at night.

Fever of mild degree is not uncommon; in civilian practice it often presents great difficulty in diagnosis and management. The temperature rarely exceeds 100.5° and is often discovered after a mild sinusitis or respiratory infection. Often it is the physician who initiates cardiac symptoms by diagnosing rheumatic fever and advising prolonged bed rest.

Other symptoms which are included in the syndrome of NCA are dizziness, sweating, cold clammy palms, nervousness, tremor, headache, flushing, frequency of micturition, insomnia, paresthesia, faintness, diarrhea, difficulty in concentration, indecision, impairment of memory and a tendency to mental, emotional and physical apathy.

Objective Signs. There are no objective signs of organic cardiac disease as a rule. But patients with NCA may independently experience rheumatic arteriosclerotic (coronary) or other cardiac disease. Furthermore the discovery of such organic heart disease may be the factor which precipitates overt symptoms of NCA.

The electrocardiogram is usually normal.[41] In some patients there is a depression or inversion of the T wave in leads II and III and in precordial leads.[24] More often the T waves are normal when the patient is recumbent and abnormal when he sits or stands. The fact that these postural electrocardiographic changes may be minimized or abolished by ergotamine suggested that they are due to sympathetic stimulation.[29, 39] The heart tends to be small,[26] but it is normal when related to the size of the thorax and body.[11, 3]

Tachycardia is common not as a result of effort but because of emotional attitudes.[19] Following exercise the pulse rate increases more than normally and its return to the original level is abnormally delayed. The blood lactate concentration is significantly higher in NCA during moderate exercise than in control subjects.[4] The vital capacity is normal but there is an increase in minute respiratory volume.[5]

Diagnosis

The diagnosis of NCA is based on the general appearance and behavior of the patient, on an analysis of the above-mentioned symptoms, and on the exclusion of organic heart disease. But the diagnosis should also be made when NCA is combined with organic heart disease by a similar analysis of the symptoms and by recognition of the lack of relationship to the type and severity of the organic disease. The diagnosis of neurocirculatory asthenia should be made not only by exclusion of organic cardiac disease but also by positive data supporting the psychologic basis of the symptomatology.

A hyperventilation test has been suggested to aid in diagnosis.[13] The duration of breathholding after hyperventilation, divided by the duration of breathholding before forced breathing, is termed the hyperventilation index. Normally it exceeds 1.3. In patients with NCA who have respiratory symptoms it is less than 1.3. Its value remains to be assessed.

Differential Diagnosis

Neurocirculatory asthenia is not infrequently treated as rheumatic fever, sinusitis, undulant fever, tuberculosis and hyperthyroidism. It is especially important not to misinterpret the symptoms as being due to organic heart disease.

Prognosis

The outlook for disappearance of symptoms and for efficient work is poor when there is a serious psychiatric background, a long history of symptoms and when the syndrome of NCA appears after relatively brief and minor strain. On the other hand a good symptomatic result may be anticipated if the syndrome appears acutely, after a prolonged and very intense emotional and physical strain in an individual without previous significant psychomotor or personality derangement. If the precipitating cause can be discovered and abolished, it is probable that the symptoms can be alleviated.

Follow-up studies of cases of NCA are difficult to evaluate and compare because cases are not analyzed according to the above-mentioned factors and because of differences in criteria of improvement or cure. Grant[16] studied 601 former soldiers with NCA about seven years after discharge. Approximately 15 per cent were free of symptoms, another 15 per cent improved, and over 50 per cent unchanged or worse. Relatively poor results were reported by Parkinson,[32] by Jones and Lewis[19] and by Raines and Kolb,[33] while others reported remarkable therapeutic results as measured by the percentage of patients returned to military duty.[6, 37, 15, 18]

Treatment

Winning and retaining the patient's confidence and cooperation are essential. This is usually accomplished by a careful and detailed history and physical examination and the demonstration of a complete understanding of and interest in the patient's symptoms. Reassurance as to the absence of organic heart disease is invaluable. The recommendation of rest is to be avoided. While it may provide the solace that comes from the avoidance or escape from life's situations, it usually fosters the very factors responsible for the disorder.

Specific treatment should be directed toward the underlying psychologic

abnormality and toward the extrinsic factors which appeared to precipitate the syndrome. When the latter occurs acutely as a result of an obvious extreme harrowing experience, reassurance as to the circulatory status and elimination of the precipitating cause are usually curative. In other acute cases without previous profound psychologic difficulties the precipitating factor is less obvious and must be sought by repeated discussions or by narcohypnosis if necessary. Elimination of the precipitating factor, when possible, and guidance of the patient in management of his problem or in his adjustment to it often yield a favorable result.

In chronic cases the discovery and control or removal of the precipitating factor are likewise helpful, but it is desirable and often essential that the total life situation of the patient and his attitudes and emotional reactions be analyzed. A revision in the patient's standards and goals, which are retained from infancy and childhood, is often valuable. An effort should be made to enhance his ego security by lowering his exaggerated and anachronistic standards by increasing his self-evaluation and by promoting his physical and intellectual capacities and his social relationships.

Treatment of individual symptoms is secondary but important. Beneficial results have been attributed to the judicious use of sedatives, vitamins, sex hormones and occupational therapy as well as to reassurance and reeducation. Reeducation should involve the formulation of and guidance in a program of physical, mental and social activity best suited to the individual's particular problems, capacities and need.

ISOLATED AND TRANSIENT FUNCTIONAL CARDIAC SYMPTOMS

Under this heading are included cases in which isolated functional symptoms such as difficulty in taking a deep breath, precordial pain or palpitation occur in an individual without apparent psychologic difficulties. As a rule he is annoyed by the symptom and may be worried about the presence of heart disease, but his efficiency at work and his interpersonal social relationships appear unimpaired.

In such cases reassurance as to the normalcy of the heart and the functional nature of the symptom often suffices to alleviate it or to render the patient unconcerned. Sometimes a change in hygiene, including more sleep and relaxation, a holiday, a bland diet and regular bowel habit, and elimination of tobacco, alcohol and coffee are helpful, especially for palpitation or submammary pain. Local infiltration with procaine may eliminate pain, at least temporarily, and convince the patient that it arises in the chest wall and not in the heart. Physical exercise, including training in abdominal (diaphragmatic) breathing, is valuable in patients with functional dyspnea. If the symptom is severe and persists despite these measures, a more fundamental psychiatric investigation and treatment are necessary.

OBJECTIVE FUNCTIONAL CARDIAC SIGNS

Under this heading are included systolic murmurs, arrhythmias, tachycardia or minor electrocardiographic abnormalities which cannot be related to any underlying organic disease. These have been discussed in connection with the above-mentioned individual conditions. Careful cardiac investigations and follow-up examinations are essential to exclude organic disease. If evidence of organic disease is absent, it is best to emphasize this to the patient,

to reassure him and to avoid restriction of activity. On the other hand, insurance examiners are often compelled to reject such individuals for insurance or to increase their premium rates on the purely statistical basis of a greater than expected mortality rate.

HEART PHOBIAS

This includes three types of cases: (1) fear of cardiac death although there are neither symptoms nor signs of cardiac disease, (2) fear of cardiac death because of functional symptoms or signs or (3) fear of cardiac death because of actual organic heart disease.

The first group presents a purely psychiatric problem and should be so handled. In the second and third groups the therapeutic mainstay is reassurance as to either the absence of heart disease in group (2) or as to the favorable outlook if the patient, in group (3), follows the physician's instructions. In all groups, avoidance of unnecessary restrictions as to physical activity supports the physician's verbal reassurance.

FAINTING AND SYNCOPE

These have been discussed in Chapter 10. They are mentioned here because many people associate fainting with cardiac disease. However, cardiac disease is responsible for only a small minority of cases, e.g., Adams-Stokes syndrome. Although emotional factors, especially fear and anxiety, may induce the common type of vasodepressor faint (p. 225), there is often no profound psychologic difficulty. If the stimulus, such as the sight of blood or an operation, is repeated several times, the syncopal response may no longer occur. In many of the patients subject to occasional faints of the vasodepressor type, there appears to be a defect of vasomotor regulation.

Hysterical fainting has been distinguished by the absence of objective changes in blood pressure, pulse or electroencephalogram. The fainting is due to a deep-seated psychologic disturbance.

Hyperventilation may produce giddiness and a faint feeling but no syncope except indirectly by inducing anxiety and a vasodepressor reflex.[8]

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PART VI

SPECIAL PROBLEMS IN HEART DISEASE

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PREGNANCY AND HEART DISEASE

Pregnancy is a physiologic process which imposes a functional load on the heart and circulation. Pregnancy is well borne by the normal heart, which calls upon its substantial reserve to supply the increased demands of the growing embryo. The response of the diseased heart, on the other hand, is not always adequate and varies with the degree of cardiac compensation before pregnancy. The well compensated heart may tolerate the increased circulatory demands of pregnancy essentially as well as the normal heart; under the same circumstances, hearts with limited reserve fail with significant frequency. Thus pregnancy is not responsible for a specific etiologic type of heart disease. But in the presence of a previously diseased heart, pregnancy may represent an intolerable circulatory burden which induces cardiac failure and death.

Preexisting heart disease is the most important complicating factor likely to endanger the otherwise smooth course of normal pregnancy and labor. According to Hamilton,[26] heart disease was present in 1.8 per cent of 76,125 pregnancies treated at the Boston Lying-In Hospital in the past twenty-five years. In other studies the incidence of heart disease in pregnant women varied between 1 and 4 per cent.[27, 34, 52] Heart disease in pregnancy almost always means rheumatic heart disease. The latter is encountered in over 90 per cent of pregnant cardiac patients, congenital cardiovascular lesions occur in about 4 or 5 per cent, while syphilitic, hypertensive and other types of heart disease are observed only occasionally.[35, 53, 26] Among the rheumatic cardiac cases, mitral stenosis alone or in combination with aortic valvular disease occurs in at least 75 per cent.

PATHOLOGIC PHYSIOLOGY OF THE CIRCULATION IN PREGNANCY

The circulation in pregnancy provides an increased volume of blood necessitated by the growing embryo. The latter augments the total metabolism of the body and consequently the consumption of oxygen. According to Cohen and Thomson[21] the *consumption of oxygen* increases between 15 and 25 per cent. But since this approximates the average weight change during pregnancy, they concluded that the *basal metabolic rate* was essentially unchanged. On the other hand, Clute and Daniels[19] stated that the basal metabolic rate in normal pregnancy was elevated as much as 25 to 30 per cent.

The *cardiac output* (minute volume) increases progressively from the fifth

to the ninth month, at which time it is usually about 50 per cent above normal.[28, 24, 51, 13] In the last few weeks of pregnancy there is an unexplained, moderate fall in the cardiac output from these maximal levels. In part, the augmented output is mediated by a slight acceleration of the pulse rate (10 to 20 beats per minute), but in large measure it is due to a greater output per beat (elevated stroke output).

The *work of the heart* is proportional to the product of the cardiac output and the mean arterial blood pressure. Since the latter is not significantly altered during pregnancy[29, 2] the work of the heart per beat and per minute are increased by as much as the cardiac output, namely about 50 per cent.[51] This additional work may represent the extent of the cardiac load of pregnancy.

The augmented cardiac output reflects a similar enhancement of the venous return to the heart. The latter is accomplished in part by an acceleration of the speed of the circulation and in part by an enlargement of the circulating blood volume. There is a progressive acceleration of circulatory speed (reduced circulation time) from the third to the ninth month of pregnancy. This acceleration diminishes moderately in the last few weeks before term.[20] While there are discordant reports regarding the circulation time,[50, 36, 17] the findings of Cohen and Thomson[20] have been recently confirmed by those of Manchester and Loube,[37] whose determinations in 48 pregnant women disclosed a progressive circulatory acceleration from an average circulation time of 12.4 seconds in the first trimester to 10.2 seconds in the third trimester.

The *blood volume*, like the cardiac output, increases progressively until the ninth month, at which time it is about 45 per cent above normal, and then falls to about 30 per cent above normal in the last month before term.[56, 1] The plasma volume increases proportionately more than the cell volume; this results in a diminished viscosity and hematocrit and may account for an apparent slight anemia.

The circulatory changes in pregnancy have been interpreted as similar to those of an arteriovenous fistula.[11] There is an almost direct connection between arteries and veins in the placenta.[49] The consequent blood shunt from the arterial to the venous side results in an acceleration of blood flow, of venous return and of cardiac output. Some support for this concept was found in observations of the circulatory dynamics during and after labor by Brown and her associates,[9] but there are many gaps in the analogy between the circulatory changes in pregnancy and those in cases of arteriovenous fistula.

The circulatory adaptations in pregnancy may be likened also to those of hyperthyroidism in that in both they are designed to satisfy increased metabolic demands—local demands in pregnancy, generalized in hyperthyroidism. In both, increased metabolism results in accelerated velocity of blood flow, which is, however, much less pronounced in pregnancy. The increased speed of circulation is insufficient to maintain the required cardiac output in pregnancy and the progressive augmentation of blood volume may be regarded as a compensatory mechanism to provide a needed increase in cardiac output. The cardiac output increases substantially more than the oxygen consumption[12] because of a subnormal arteriovenous oxygen difference, the latter a probable consequence of the accelerated speed of circulation.

While the increased circulating blood volume and the augmented venous return are thus viewed as adaptive mechanisms, their disadvantages must also be considered. Like exercise, saline infusions and other factors which enhance

the venous return, the load of pregnancy imposes no serious strain on the normal or well compensated heart. The diseased heart, with diminished functional reserve, may be unable to maintain an adequate cardiac output despite the enlarged blood volume. Further increases in blood volume cannot be normally propelled by low-reserve hearts. The consequence is a congestion of the lungs, viscera and other tissues behind the failing chambers. Since the accelerated blood flow, the augmented blood volume, venous return, cardiac output and work of the heart all become significantly greater after the fourth or fifth month and reach their maximum in the ninth lunar month, the intervening period represents the span of increasing danger to the cardiac patient. There is in fact a close correlation between the time of onset of heart failure and the severity of the circulatory load.[27]

Circulatory Dynamics of Labor. As compared with the prolonged and increasing strain of pregnancy, that of labor is relatively well tolerated. It has been mentioned that the blood volume, cardiac output and work of the heart diminish significantly in the four weeks before term. Labor itself is associated with a moderate, transient elevation in arterial blood pressure, and a corresponding increase in the work of the heart.[46] But the level attained is less than the maximum of pregnancy. A rise in venous pressure in the first twenty-four hours after delivery has been attributed to the effects of ergotrate.[9] That the strain of normal labor is less than that of pregnancy is supported by the infrequency of heart failure beginning during or immediately after delivery. On the other hand, if heart failure is already present when labor starts, there is a great risk of intensifying the myocardial insufficiency.

CARDIOVASCULAR MANIFESTATIONS DURING PREGNANCY

An evaluation of the cardiac status should take into account the frequency of cardiac symptoms and signs in pregnant women even without heart disease. These may simulate the manifestations of organic heart disease and heart failure.[48]

Dyspnea on exertion and orthopnea are common complaints, especially in the latter half of pregnancy. These symptoms are not due to a reduction in vital capacity, for careful studies have disclosed that the vital capacity remains unchanged or increases slightly during the course of pregnancy.[55] However while the vital capacity remains normal, the total pulmonary ventilation is increased as much as 57 per cent.[3] This denotes that adequate ventilation is maintained only by increased work of the respiratory muscles—which could account for the sensation of dyspnea. The dyspnea of pregnancy may be analogous to the noncardiac dyspnea which occurs in obese individuals or in those who gain weight rapidly. Often the dyspnea of pregnancy takes the form of sighing respiration or of inability to take a deep breath, a disturbance of psychic origin. In any event, neither exertional dyspnea nor orthopnea is to be regarded as certain evidence of heart failure without careful evaluation (p. 61).

Palpitation and tachycardia are frequent with or without associated dyspnea. Respiratory distress, choking sensations and palpitation occurring at night may simulate an attack of paroxysmal nocturnal dyspnea. But cough with frothy or blood-stained sputum and pulmonary râles are not noted. There may be transient basal râles due to compression of the lung by the elevated diaphragm, but these disappear after cough or a few deep respirations.

Edema of the legs develops in about 25 per cent of noncardiac pregnant women, especially during the last two months of pregnancy. The association of dyspnea and edema is likely to suggest the possibility of heart failure. But the edema is a local phenomenon confined to the lower extremities. It is due to compression of the iliac veins by the enlarged uterus and its contents. While an extremely high venous pressure in the lower extremities is probably the chief cause of the dependent edema, the enlarged circulating blood volume, a diminished concentration of blood proteins and of osmotic pressure, and local tissue changes may be contributory factors. That the edema is not due to heart failure may be perceived from the absence of venous engorgement in the cervical veins, and from the normal venous pressure in the upper half of the body.

Cardiac enlargement may be diagnosed because the apical impulse is displaced to the left and upward by the elevated diaphragm. Roentgenologic examination occasionally suggests slight cardiac enlargement, but the area and volume of the heart increase only in proportion to an increase in the corresponding dimensions of the chest.[7] Allowance should be made for the tendency to overestimate the size of the heart on physical examination and the difficulties of such examination due to the enlarged breasts. Hollander and Crawford[32] were impressed by the cardiac indentation of the anterior wall of the esophagus.

A *systolic murmur* is audible at some time during pregnancy in most women. Usually it is in the pulmonic or apical regions. Diastolic murmurs should be considered as evidence of organic heart disease unless proven otherwise. A third heart sound is frequently audible and may simulate the gallop rhythm of heart failure. The second pulmonic sound is often loud and may be accentuated and reduplicated. A slight tachycardia is the rule. Premature beats are not uncommon. A collapsing pulse and capillary pulsation may accompany a wide pulse pressure in the absence of aortic valvular disease.

The *electrocardiogram* usually shows a left axis deviation and an inversion of T_3.[47] These are due to the transverse position of the heart and resemble the findings in the electrocardiogram of obesity. A deep Q_3 as well as the inverted T_3 is encountered in a small percentage of cases and is probably due also to the altered position of the heart.[15, 32]

DIAGNOSIS OF CARDIAC DISEASE IN PREGNANCY

The recognition of organic heart disease, when present, is essential for the proper management of the pregnant woman. Due care must be taken not to mistake the above-mentioned findings in pregnancy for cardiac disease.

Often a careful history will reveal that the patient has some organic cardiac lesion and simple physical and fluoroscopic examination readily confirms this information. But occasionally a previous diagnosis of heart disease may be found to be inaccurate. On the other hand, the absence of a history of rheumatic fever or the failure of previous routine examinations to disclose a cardiac disease should not be accepted as proof that the heart is normal.

Since the common heart disease of pregnancy is rheumatic heart disease, careful search should be made for evidence of mitral or aortic valvular disease. The crescendo presystolic murmur of mitral stenosis may be overlooked unless the patient is examined in the left lateral (decubitus) position, prefer-

ably after exercise. The murmur may be sharply localized to the apex. The diastolic murmur of aortic insufficiency is often best heard along the left sternal border with the patient standing and with the breath held in expiration. A loud systolic murmur may be due to rheumatic aortic stenosis; a systolic thrill should be sought carefully. In its absence, pulse tracings may confirm the diagnosis.

Fluoroscopic examination may provide the first clue or the confirmatory evidence of heart disease. Cardiac enlargement should be unequivocal to be diagnostic in itself. The localization of the enlargement may be especially significant, e.g., the left auricle and the pulmonary salient in mitral stenosis and the left ventricle in association with dynamic pulsations of the ventricle and aorta in cases of aortic insufficiency.

The possibility of *congenital heart disease* should be considered. The machinery-like murmur of a patent ductus arteriosus is distinctive. Coarctation of the aorta may be suggested by the presence of hypertension or an unexplained loud systolic murmur, especially in the left posterior chest. Subaortic stenosis may be suggested by a loud aortic or pulmonic systolic murmur and thrill since infancy, and by left axis deviation in the electrocardiogram. Tetralogy of Fallot has rarely been encountered in pregnancy, but more patients with this condition may live to maturity and become pregnant if the Blalock operation fulfills its present promise (p. 656).

In summary, the recognition of cardiac disease in pregnancy requires a careful physical, fluoroscopic and sometimes an electrocardiographic examination. A diastolic murmur and distinct cardiac enlargement are the chief diagnostic features. The cardiac enlargement is most suggestive if it involves distinct contours of the heart, which can then be related to corresponding valvular lesions and murmurs. In the presence of loud systolic murmurs, a diagnosis of organic heart disease depends on confirmatory findings such as thrills, unequivocal cardiac enlargement or collateral evidence of congenital heart disease.

DIAGNOSIS OF HEART FAILURE

Having distinguished the cardiac patient in pregnancy, the physician must make careful observations for the development of heart failure. Since dyspnea on exertion and orthopnea occur during pregnancy without heart disease, their usual merit as early clues of heart failure is somewhat vitiated. Nevertheless, by careful history and observation the physician may justly conclude that the dyspnea is out of proportion to that attributable to pregnancy and is in fact caused by heart failure. Unexplained cough, especially that which occurs on effort, is also a valuable early clue to the possible occurrence of heart failure. Breathlessness may awaken the patient from sleep or it may occur after intercourse. The association of cough with frothy or blood-tinged sputum and with persistent rhonchi or moist râles in the chest denotes that the dyspnea and cough are due to left-sided heart failure. Relief of the dyspnea and the cough following extreme restriction of salt and one or two injections of mercurial diuretics is a valuable diagnostic test to confirm the diagnosis of heart failure.

Objectively, heart failure may be first discovered by serial determinations of vital capacity, which is normal in uncomplicated pregnancy. In the presence

of pulmonary congestion due to left-sided heart failure, there is usually an unequivocal reduction in vital capacity. While the determination of vital capacity has many limitations, it is of value if the patient is intelligent and cooperative and has been taught to perform the test, and if successive tests are compared at regular intervals. Nevertheless, it is not a practical routine procedure. As a rule, the earliest sign of congestive heart failure is the development of persistent râles at the bases of the lungs. The lungs should therefore be examined regularly and carefully in all cardiac patients throughout pregnancy.

Of course there is usually no difficulty in determining the presence of heart failure when the complete clinical picture is unfolded. The patient is dyspneic on the slightest exertion or at rest. Complete recumbency is intolerable because of respiratory distress. Mild or moderate cyanosis is common in patients with mitral stenosis and heart failure. Râles are readily audible throughout the lower portions of the lungs. Hydrothorax may be present. The cervical veins become engorged. The liver is enlarged and tender. Edema of the lower extremities is pronounced.

PROGNOSIS OF CARDIAC DISEASE ASSOCIATED WITH PREGNANCY

Pregnancy involves a greater risk for the cardiac patient than for the normal individual. However, with increasing knowledge and attention to the problems of the cardiac patient, the mortality rate during pregnancy has been substantially reduced. From quoted figures of 40 to 55 per cent mortality at the turn of the century, the rate dropped to 15 per cent in the first three years after the formation of the Heart Clinic at the Boston Lying-In Hospital in 1921, to 5 per cent between 1925 and 1927 and to 2 or 3 per cent between 1937 and 1939.[27] The overall maternal death rate among cardiac patients in the past twenty-five years was 3.9 per cent.

Although the maternal death rate is still about five times as high as among noncardiacs, it is perhaps as important to emphasize the 97 or 98 per cent chance of survival among cardiac patients who are pregnant as to stress the greater risk among these patients. Furthermore, the mortality rate among pregnant cardiacs should be compared with that of nonpregnant cardiacs in the same age range, for the expected mortality among cardiacs is higher than that of noncardiacs, independent of pregnancy. It appears likely that if the obviously decompensated patient is restricted from becoming pregnant, and if the compensated cardiac patient is carefully managed to avoid heart failure during the course of pregnancy or is properly and promptly treated if heart failure does develop, then the maternal mortality rate among pregnant cardiacs need not significantly exceed that among noncardiac pregnant individuals nor that among comparable cardiac patients who are not pregnant. This, of course, is an ideal which has not been quite attained.

The prognosis among cardiac patients during pregnancy conforms remarkably with that anticipated on the basis of cardiac functional classifications made at the onset of pregnancy. Utilizing the functional classification of the New York Heart Association, Pardee[40] observed the following mortality in the various classes:

Class I. Patients with organic heart disease who suffer no limitation of activity. There were no deaths among 157 patients in this category.

Class II A (now Class II). Patients with heart disease who suffer slight or

moderate limitation of activity. There was 1 death among 180 patients in this group.

Class II B (now Class III). Patients with heart disease who experience moderate to great limitation of physical activity. Less than ordinary physical activity causes discomfort. There were 8 deaths among 169 such patients.

Class III (now Class IV). Patients with heart disease who are unable to carry on any physical activity without discomfort. There were 16 deaths among 40 such patients.

These and other observations indicate that pregnancy is tolerated without significant additional risk by the well compensated patient with heart disease but that the mortality rate increases as the degree of compensation diminishes. Carr and Hamilton[14] and Hamilton and Thomson[27] found that an unfavorable outcome might be anticipated among those cardiac patients who present (1) signs of heart failure or a history of heart failure, (2) a serious disorder of the heart beat such as auricular fibrillation, (3) a complicating serious disease such as diabetes, pulmonary tuberculosis, nephritis. Among 95 cases classified as "unfavorable" on the basis of these criteria, when first seen, the maternal mortality rate was 16.7 per cent in contrast with a mortality rate of 2.3 per cent among 655 cases which were classified as "favorable" because they did not satisfy these criteria. Patients with auricular fibrillation suffered the notably high mortality rate of 33⅓ per cent. It is chiefly because of pregnancies among cardiac patients with poor cardiac reserve or actual heart failure that the maternal mortality is relatively high among subjects with heart disease. According to Stromme and Kuder[53] heart disease still accounts for 24.33 per cent of all maternal deaths in pregnancy at the New York Lying-In Hospital.

If the patients who develop congestive heart failure during pregnancy, labor or the puerperium are omitted from consideration, it is doubtful whether pregnancy has any ultimate deleterious effects on longevity or mortality rates.[34, 8] The studies of Friedberg and Tartakower[23] and of Reid[43] indicate that if the pregnancy itself is well tolerated, there is no shortening of the life of cardiac patients, even after bearing many children.

Congestive heart failure is the commonest serious complication of pregnancy in cardiac patients and the most frequent cause of death.[10] Its likelihood of occurrence is greater, the less the cardiac reserve of the patient, as evaluated at the onset of pregnancy. Cardiac failure occurs more frequently in cardiac patients who become pregnant after the age of thirty-five than in those below that age level. The incidence of heart failure increases sharply after the fifth month of pregnancy and progressively thereafter to the ninth month, corresponding to the similar increase in physiologic strain as described above. With the reduction in circulating blood volume and cardiac output in the last two to four weeks of pregnancy, there is a corresponding diminution in the occurrence of heart failure. According to Gorenberg and McGleary,[25] 80 per cent of 77 cases of heart failure developed before the last month of pregnancy. Acute heart failure beginning during the course of labor is uncommon, but heart failure that is already present may be intensified. The majority of deaths from heart failure occur during the puerperium, but careful history and observation disclose that the onset of heart failure in such instances usually occurred during the course of pregnancy.

Of the other complications of pregnancy in cardiac patients *subacute bac-*

terial endocarditis is one of the most important.[22] The early use of penicillin or streptomycin in adequate dosage should minimize the mortality from this disease. *Pulmonary embolism,* infection, toxemia and hemorrhage are complications in noncardiac as well as cardiac patients, although embolism may occur more frequently in the latter. With the inauguration of early ambulation and the use of anticoagulants or of venous ligation, the frequency of and mortality from pulmonary embolism may be sharply reduced. Postpartum infection has already diminished as a cause of death since the use of antibiotics.

Among the hazards that cardiac disease adds to pregnancy is the *higher fetal mortality* than among normal pregnant women. In the Boston Lying-In Hospital the fetal mortality among favorable cases in the past ten years[26] was 8.6 per cent. However, among unfavorable cardiac cases the infant mortality was still relatively high at 31 per cent, while among patients with auricular fibrillation the infant mortality was about 50 per cent. According to Stromme and Kuder,[53] maternal heart disease does not adversely affect infant mortality, but no detailed analyses are presented. But Bunim and Rubricius[10] found that the infant mortality rate for their group of patients with congestive heart failure was three times as high as for patients with compensated heart disease and four times as high as for normal pregnant women delivered on the same obstetrical service. The chief cause of infant mortality among cardiac patients is prematurity and stillbirth. Some of this is due to the unwise practice of interrupting or inducing labor before the thirty-fifth week. From the viewpoint of the child as well as the mother, the risk of labor diminishes in the last month of pregnancy. There is evidence also that infant mortality is less when delivery occurs through the pelvis than when cesarean section is performed.[18] The use of low forceps instead of entirely spontaneous delivery may also diminish the risk to the infant.[54]

There are insufficient data to formulate prognostic principles for each of the rarer forms of heart disease encountered in pregnancy. In general, as in rheumatic heart disease, the risk increases as the degree of cardiac reserve or cardiac compensation diminishes. Thus well compensated patients with patent ductus arteriosus, coarctation of the aorta,[4] septal defects or congenital heart block[5, 42] may successfully consummate one or more pregnancies. But in these as in rheumatic cardiac patients, despite favorable assessment of the cardiac status, there is always a risk of the sudden and unexpected development of acute heart failure during pregnancy, labor or the puerperium.

Patients with chronic glomerulonephritis without azotemia and patients with mild essential hypertension assume only a slight risk with pregnancy. Patients with severe hypertension and significant cardiac enlargement and those with azotemia assume a risk equivalent to that of patients with unfavorable rheumatic cardiac disease.[16, 45] In addition there is some evidence that hypertensive patients have a higher than normal incidence of eclampsia and that the progress of hypertension is hastened by pregnancy.[30, 44] Attacks of paroxysmal dyspnea or pulmonary edema with extreme rise in blood pressure may necessitate an interruption of pregnancy but extreme restriction of sodium and fluids, the administration of morphine, rest, digitalization and diuretics may prevent or control the attacks. A case of coronary occlusion followed by pregnancy with successful termination has been reported by Horwitz and associates.[33]

THE MANAGEMENT OF HEART DISEASE AND HEART FAILURE IN PREGNANCY

The major problem in the treatment of the cardiac patient during pregnancy is the prevention and control of heart failure.[31] To this end it is essential that the presence of cardiac disease be recognized early. The subject with such disease must be registered with her physician early in pregnancy and regular visits at two- to four-week intervals should be made, depending on her cardiac status and symptoms. Cooperation with a cardiologist or with an internist interested in the problems of cardiac disease in pregnancy is desirable. Cardiac patients should enter the hospital one to two weeks before the expected date of delivery for proper appraisal of the cardiac status, planning of delivery procedure and for the institution of treatment of incipient heart failure if necessary.

The well compensated cardiac patient (Class I and some in Class II) requires little restriction in activity except for severe and unusual physical exertions. A rigid restriction in sodium intake appears desirable, especially after the fourth calendar month. A moderate restraint in weight gain also appears advantageous. Digitalis is not given as a prophylactic measure in this group of patients. In these as in all other cardiac patients excellent hygienic care, including adequate periods of rest and of sleep, attention to proper dietary intake and especially the avoidance of upper respiratory and other infections should be stressed. A supplementary intake of Vitamin B_1 may be necessary because of the added requirements of pregnancy and the possible contributory role of thiamine deficiency in heart failure.[6]

Cardiac patients whose outlook is less favorable because of a poorer cardiac reserve (Class III or Class IV and some in Class II of the New York Heart Association) or those with a previous history of congestive heart failure require greater restrictions as to physical activity and more rigid regulation. In some instances modified bed rest most of the day or rest in a chair or chaise longue may be necessary throughout pregnancy. The intake of sodium should be reduced to 2 gm. or less daily if possible. Digitalis should be continued if started during a previous episode of heart failure. Patients in this group of limited cardiac reserve should be hospitalized at least two weeks before term according to the requirements of the individual case. Patients in Class III or IV usually require digitalization.

If heart failure develops in any patient or is already present when the patient is first seen, active treatment should be instituted as described above (Chapter 9). Bed rest, at home or in the hospital, is usually necessary. Digitalization should be effected and maintained. Sodium intake should be restricted to 1 gm. daily. Mercurial diuretics should be administered every two to seven days according to the need and response. If there is evidence of infection, thiamine deficiency, anemia or hypoproteinemia which might contribute to the development of heart failure, these factors should be eliminated or corrected by appropriate measures. The intravenous introduction of fluids containing sodium (saline, plasma, blood) should be avoided.

In the presence of heart failure during the first three months of pregnancy, the patient should be aborted by dilatation and curettage after several days of treatment to control the heart failure. From the third to the fifth month abortion by abdominal hysterotomy should be performed only if there is frank

evidence of heart failure. Tubal sterilization may be indicated at the same time. Thereafter labor should not be induced until after eight to eight and one half calendar months have elapsed, i. e., until after the drop from the peak of the circulatory burden. It is unnecessary to terminate pregnancy before term in order to avoid the strain of labor since heart failure rarely begins in labor and since the strain of labor is less than that of pregnancy in the eighth calendar month.

Labor should be permitted to proceed normally in the cardiac patient. Vaginal delivery is allowed even in patients with serious heart disease unless there are noncardiac indications for cesarean section. Even in the presence of heart failure it is uncertain that a cesarean section with sterilization should be preferred to delivery from below with sterilization at a later date if desirable. The present trend is definitely against interruption of pregnancy in the later months of pregnancy and against cesarean section during labor, for both the maternal and fetal mortality rates are significantly less when normal delivery by the vaginal route is permitted.[38, 25] However, it is desirable to avoid a prolonged second stage by the use of the low forceps procedure. According to Mendelson and Pardee,[39] the elevation of the pulse rate above 110 and of the respiratory rate above 24 during the first stage of labor provide usually reliable clues to impending heart failure and the need for appropriate therapeutic measures.

The competent administration of anesthesia by an experienced anesthetist is important in minimizing the strain of labor. Ether is generally regarded as one of the safest anesthetics and best tolerated by cardiac patients. Nitrous oxide and oxygen and ethylene and oxygen may be employed only for the preliminary induction of anesthesia, but even then the most diligent care should be taken to avoid asphyxia. Cyclopropane with oxygen and chloroform have been shunned by many because of their possible cardiac depressant effects. Preanesthetic medication may be given to the cardiac patient as to the normal individual in the first stage of labor.

Acute pulmonary edema is a sudden and sometimes startling incident which occurs sufficiently often during pregnancy or labor to require special mention. It is usually a complication of mitral stenosis and may occur in apparently well compensated patients and without apparent cause. But often it is induced by the intravenous administration of fluids.[41] Acute and terrifying dyspnea, with or without cyanosis, cough, frothy sputum and hemoptysis, are the outstanding manifestations. Recurrences during the course of pregnancy are not uncommon.

The prompt administration of morphine may in itself control the attack. The slow intravenous administration of 0.25 to 0.5 gm. (3¾ to 7½ grains) of aminophylline in 10 to 20 cc. of saline may also abort the attack. Digitalis or ouabain should be given intravenously (p. 187). Venous tourniquets should be applied to all four extremities and if this is ineffective a venesection should be performed. If the attack is protracted, oxygen should be administered by mask or tent. To prevent recurrences sodium intake should be curtailed drastically, digitalization should be maintained, aminophylline rectal suppositories (0.5 gm. aminophylline) should be inserted before retiring and mercurial diuretics administered at appropriate intervals. The prophylactic use of morphine in the twelve hours following labor may prevent the occurrence of postpartum pulmonary edema. Similarly, administration of penicillin

may be advisable immediately preceding and following labor to avoid the occurrence of bacterial endocarditis.

INDICATIONS FOR DISCOURAGING PREGNANCY AND FOR PERFORMING THERAPEUTIC ABORTION

The physician is frequently confronted with the question of advising women with heart disease whether they may safely undertake pregnancy and childbearing or whether they may continue if already pregnant. Often there are associated religious, socioeconomic and personal factors which may be decisive regardless of medical considerations. The physician's advice should consist chiefly in providing his patient with the known data as to prognosis, especially as applied to her own cardiac status. Having been apprised of the facts, she herself must decide whether her desire for a child outweighs the probable risk.

In summary, pregnancy may be undertaken by the well compensated cardiac patient with only slightly more risk than by the normal woman. The mortality risk during the childbearing age is essentially identical whether she becomes pregnant or not. In borderline cases she is more justified in undertaking pregnancy if it is the first or second than if there are already two or three children. Pregnancy should be undertaken and the family completed relatively early in life since the diseased heart becomes less capable of tolerating the load of pregnancy with advancing years. However, the woman with rheumatic heart disease who marries before she is twenty-one might advantageously delay pregnancy for two or three years, since the risk of activation of a quiescent rheumatic infection diminishes progressively after the age of twenty-one.

Patients whose outlook is relatively unfavorable (i. e., those in Classes III and IV and some in Class II of the New York Heart Association Classification, or those with signs or a history of heart failure, auricular fibrillation or a complicating serious disease), should be impressed with the great risk of pregnancy: maternal mortality of 15 to 18 per cent, fetal mortality of 30 per cent. If pregnancy is nevertheless undertaken, the importance of early and constant cardiac supervision and of rigid adherence to a prophylactic and therapeutic regime must be stressed.

If the problem is one of terminating rather than of undertaking pregnancy, advice varies according to the duration of pregnancy, and to religious and legal considerations, as well as the clinical status of the patient. Although the risk to life among well compensated patients (Class I) is only slightly enhanced by pregnancy, under special circumstances abortion by cervical dilatation and curettage is permissible during the first two months if the patient desires to terminate the pregnancy. This is particularly advisable if there are already three or more children or if the responsibilities involved in raising a family are likely to endanger the patient's health. After the first two or three months of gestation the risk of artificial termination of the pregnancy is probably greater in the well compensated cardiac patient than is the completion of term and delivery.

Among "unfavorable" cases, i. e., with limited compensation or with evidence or history of cardiac failure, termination of pregnancy should be encouraged if the patient is seen in the first five months of pregnancy. This can be done from below in the first two months, or by abdominal hysterotomy

from the third to the fifth month. Thereafter the risk is less if the patient is treated for her cardiac disability and allowed to go to term. But even in this unfavorable group, the religious, ethical or personal beliefs of the patient may be such that pregnancy is continued despite the risks entailed.

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SURGICAL PROCEDURES IN THE CARDIAC PATIENT

An evaluation of the cardiovascular status is a traditional prerequisite to a contemplated major surgical procedure involving a general anesthetic. Implicit in such precaution is the belief that a major surgical operation and general anesthesia impose an unusual strain on the circulation, and that the diseased heart is more vulnerable to this strain than the normal heart. The internist or cardiologist is therefore frequently called preoperatively, not only to determine the cardiac status but also, if a cardiac lesion is present, to advise whether this lesion alters the decision to operate or the surgical management.

Primarily the surgeon and the patient are interested in the ability of the diseased heart to withstand the proposed operation. An estimate of this ability requires a knowledge of the risk added by the cardiac disease to the usual risk of the operation itself. The cardiologist must also estimate the general outlook and life expectancy of the patient in terms of his cardiac disease. For a substantial surgical risk cannot be justified if the cardiac condition precludes a sufficient survival period to enjoy the benefits of the surgical procedure.

The cardiologist must give consideration to the surgical condition as well as to the cardiac status, for occasionally he will discover that the so-called "surgical condition" is actually a "medical" manifestation of the diseased heart, e. g., abdominal manifestations of myocardial infarction, rheumatic fever or subacute bacterial endocarditis. The dangers of the disease for which operation is being proposed and the disability of the disease must also be carefully assessed, for an evaluation of surgical risk to a cardiac patient assumes significance only by balancing this risk against the risk and disability if operation is withheld. Finally, aside from the surgical condition itself, the particular procedure which is contemplated, the available facilities and the skill of the surgeon and anesthetist are variable factors which must be estimated before the surgical risk to a cardiac patient can be properly evaluated. Small differences in morbidity and mortality rates with different surgeons or operative procedures on the noncardiac patient may become strikingly exaggerated in the patient with heart disease.

When the decision to operate on a cardiac patient has been made, the cardiologist may be helpful in reducing the surgical risk by the correction or

alleviation of heart failure or by other preoperative measures. He may also be consulted on the choice of anesthetic agents and on circulatory problems which arise in the course of operation and postoperatively.

In general it may be stated that the cogency of the surgical indication is usually more important than the cardiac status in determining whether an operation should be performed. In the vast majority of cases the cardiac lesion is no contraindication to a necessary operation. For practical purposes the compensated heart which permits a reasonably normal, if somewhat restricted, way of life is virtually as capable of handling a major operation and a general anesthetic as a normal heart and the surgical mortality rate is not substantially higher.[11, 8] In the presence of heart failure or other serious manifestations of heart disease, however, the evaluation of the surgical indication as against the surgical risk often presents a difficult problem.

CIRCULATORY RISKS IMPOSED BY SURGICAL PROCEDURES

The commonest surgical risks which may adversely affect the diseased circulation are hemorrhage and shock, infection and thromboembolism. When these complications are severe and uncontrolled, they are equally fatal in the cardiac and noncardiac patient. In borderline cases, however, the presence of cardiac disease may turn the tide against recovery.

Cardiac hypertrophy is the usual compensation for many forms of cardiac disease. The effectiveness of this compensation depends on the maintenance of an increased supply of oxygen and nutriments to the enlarged heart by way of the coronary vessels. Hemorrhage is a serious threat to this compensatory mechanism because it may seriously compromise cardiac nutrition and oxygenation. Degrees of myocardial anemia which could be tolerated by the normal heart might result in irreversible and serious myocardial damage or in fatal cardiac disturbance when the heart is already enlarged or suffering from advanced coronary artery disease. Furthermore hemorrhage is a common cause of surgical shock with its attendant hypotension. The hypotension reduces the coronary blood flow, an occurrence which is distinctly less well tolerated by the diseased and enlarged heart than by the normal heart. Similarly shock due to other surgical causes besides hemorrhage (p. 218) poses a greater hazard for the heart with valvular, coronary or other myocardial disease.

Aseptic technic and the availability of modern chemotherapeutic and antibiotic measures have greatly reduced the incidence and dangers of postoperative infection but such infection has not been entirely eliminated, and the cardiac patient is more apt to suffer or succumb than the patient with a normal heart. Infection is one of the common precipitating causes of heart failure in the cardiac patient.

Thromboembolic disease following operations is a serious hazard to all patients but it occurs with much greater frequency among those with heart disease than among noncardiac patients (p. 871). Furthermore theoretical considerations and clinical experience indicate that thromboembolic complications are more apt to cause serious circulatory disturbances or death in the cardiac patient.

Despite the greater hazard of these surgical complications to the cardiac patient, it must be emphasized that their incidence is relatively low and not much higher in the cardiac than in the noncardiac patient. The severity of the

complication itself rather than the presence or absence of heart disease usually determines its clinical outcome. For these reasons, when proper care and skill are employed, the additional cardiac strain imposed by a surgical operation is only infrequently of decisive importance.

CARDIAC RISKS IMPOSED BY ANESTHESIA

When chloroform is used, the danger of anesthesia depends in part on the possibility of cardiac damage by direct action of the anesthetic on the heart muscle. As a rule, however, the risk of anesthesia is related to the danger of anoxemia, cardiac reflexes or sharp changes in blood pressure.

Anoxemia may result from the low oxygen concentration in the anesthetic mixture or from reflex chemical or mechanical causes interfering with respiration or the respiratory airway. The damaged, enlarged heart, especially the heart with diminished coronary reserve, is particularly susceptible to anoxemia, which may induce myocardial necrosis or predispose to ventricular fibrillation.

Cardiac standstill due to ventricular fibrillation or to vagal (carotid sinus) reflexes may occur during the induction of anesthesia or during the operative procedure. These complications are more apt to occur in patients with certain types of cardiac disease, especially those with severe coronary arteriosclerosis, calcific aortic stenosis or syphilitic coronary ostial stenosis.

A sharp reduction in blood pressure, such as often accompanies spinal anesthesia, may seriously impair the coronary blood flow in susceptible cardiac or hypertensive patients. The excitement and struggling associated with the induction of anesthesia may increase the work of the heart not only by elevating the blood pressure but also by causing an increased outpouring of epinephrine. The latter may be especially detrimental to patients with low coronary reserve.

These anesthetic complications occur with such rarity in the experience of skilled anesthetists that the theoretically greater danger to the cardiac patient is insignificant in absolute terms. Therefore they are rarely a determining factor in the decision as to operation or in the operative risk.

THE TYPE OF OPERATION

There are insufficient data to permit statistically valid generalizations as to the added risk of associated heart disease in various individual operative procedures. However, the reported observations in relatively small series of cases as well as personal clinical experience are the bases for the following impressions and opinions.

Minor Procedures. Such procedures as are usually performed with local procaine anesthesia on ambulant patients in the physician's office or in the outpatient department of a hospital can usually be performed on cardiac patients of all types without significantly greater risk than on noncardiac patients. Most dental extractions are included under this heading provided that multiple extractions are not performed at one sitting. But even multiple simultaneous extractions may be permissible under certain circumstances in well compensated cardiac patients.

Operable Malignant Neoplasms. These almost always demand early surgical intervention if there is a chance of cure and the cardiac condition is not in a terminal stage.

Emergency Operations. Operation is essential regardless of the presence of heart disease if the surgical condition is one which is otherwise rapidly fatal. Such conditions include certain forms of acute and massive hemorrhage, perforation of a viscus, cases of acute cardiac tamponade not relieved by medical means, strangulated hernia, acute phlegmonous appendicitis, ovarian cyst with torsion of the pedicle, and certain mechanical forms of acute intestinal obstruction.

Acute suppurative or gangrenous cholecystitis may also be included in this category of emergency operations but conservative treatment is sometimes warranted if careful observation discloses regression of clinical features. The use of aureomycin and other newer antibiotics may eliminate some of these cases from the category of surgical emergencies, especially when there is associated cardiac disease.

Peripheral embolism usually denotes underlying cardiac disease. Despite the added risk due to the latter, a surgical attempt to remove the embolus is indicated if it involves a major artery and threatens gangrene or death.

Elective Operations. It is not always certain whether a contemplated operative procedure is essential or elective. When it is elective, the ordinary risk of the operation plus the added risk due to associated cardiac disease must be weighed against the risks and discomforts of conservative treatment and the disability due to the surgical condition itself.

Urinary obstruction due to prostatic hypertrophy and other urologic diseases are among the commonest conditions in cardiac patients for which operation is performed.[16] The surgical and cardiac risks are further complicated by the relatively advanced age of these patients, which averages between sixty-five and seventy years. Arteriosclerotic (coronary) heart disease is common. Postoperative coronary occlusion is not rare. In a series reported by Morrison[13] the mortality rate for various forms of prostatectomy or suprapublic cystotomy averaged 19 per cent in 125 operations on cardiac patients as against 7.5 per cent in 823 such operations on noncardiac patients.

As a rule prostatectomy for prostatism is indicated in cardiac patients only if there are episodes of complete obstruction, if there is severe retention with secondary infection or impairment of renal function, or if frequency, nocturia or overflow incontinence is intolerable. Transurethral resection appears to be the operation of choice when the surgeon is skilled in this procedure and the estimated weight of the prostate does not substantially exceed 50 gm. In patients with advanced heart failure or minimal outlook for life, repeated catheterization and the use of antibiotics may be preferable to operation. But when the surgical indications are clear-cut, the surgical risk must be considered relatively moderate in most cardiac patients. Among other urologic conditions, occasionally demanding operative intervention despite coexisting cardiac disease, special mention may be made of urinary calculus with obstruction.

Operations on the Biliary Tract. The urgent surgical indication in most cases of acute suppurative or gangrenous cholecystitis has been mentioned. Obstructive jaundice due to a common duct stone almost always demands surgical intervention, but delay is sometimes justified either to confirm the diagnosis or in patients with serious cardiac disease to await the possibility of spontaneous passage of the offending calculus or calculi.

Cholelithiasis and chronic cholecystitis, which are only discovered by

roentgenologic examination and are virtually asymptomatic, are probably best treated by moderate dietary restriction. If there are severe persistent symptoms, especially frequent attacks of biliary colic despite medical treatment, cholecystectomy is usually clearly indicated even in the presence of cardiac disease. If the patient is relatively young and the cardiac disease well compensated, a cholecystectomy may be desirable even if the symptoms are fairly well controlled by onerous dietary restrictions. Under such circumstances the risk of early cholecystectomy may be less than that of delaying the operation and being forced to do it when the patient is much older and the cardiac status much less favorable.

Other common elective operations in cardiac patients include hernioplasty and hemorrhoidectomy. These operations are usually well tolerated by cardiac patients unless there are serious cardiac complications. Therefore if the disability of the hernia, hemorrhoids or other elective surgical condition is great, the operation should be performed before advancing age and the progress of the cardiac disease greatly enhance the risk. If the cardiac status is poor and the operative indication is not compelling, conservative therapeutic measures should be employed.

Thyroidectomy for hyperthyroidism has hitherto been essential in cardiac patients, even in the presence of heart failure. While the results were usually brilliant, the operative mortality was substantially greater than in noncardiac patients with hyperthyroidism. Therefore at the present time treatment should be carried out with radioactive iodine followed by a brief period of lugolization until the radioactive iodine becomes effective. Similarly in cases of fibroid uterus with excessive bleeding radiotherapy should be employed instead of hysterectomy if there is serious heart disease.

Cardiac operations have been discussed, particularly in the chapter on congenital heart disease. Poor cardiac function or congestive heart failure is no contraindication if the operative procedure is designed to diminish cardiac strain or promote aeration of the blood. This applies to release of the heart in constrictive pericarditis, to correction of a patent ductus arteriosus or arteriovenous aneurysm, or to the amelioration of tetralogy of Fallot or advanced mitral stenosis. When cardiac function is good, correction of such lesions as coarctation of the aorta, patent ductus or arteriovenous aneurysm is justified by the unfavorable natural course of these conditions.

THE TYPE OF CARDIAC DISEASE AND FUNCTIONAL CARDIAC STATUS

The surgical indication is usually a more important factor than the presence or absence of heart disease in deciding upon an operative procedure. But in so far as cardiac disease adds to the surgical risk, both the status of cardiac function and the etiologic type of heart disease are determining factors. In general there is statistical evidence to indicate that rheumatic heart disease is associated with a lower mortality than arteriosclerotic (coronary) heart disease or syphilitic cardiovascular disease.[8, 13]

Rheumatic Heart Disease. The risk of surgical procedures in rheumatic patients resembles that of pregnancy in such patients, in that there is a close correlation to the functional state of the heart. The well compensated rheumatic cardiac patient tolerates surgical operations virtually as well as the normal individual.[11, 15] The risk rises substantially in those who have experienced an attack of heart failure or those who are suffering from heart failure

at the time of operation.[13] A careful clinical history with special reference to dyspnea, cardiac asthma and orthopnea, exercise tolerance and previous episodes of heart failure is essential for a satisfactory evaluation of cardiac function.

Patients with calcific aortic stenosis are susceptible to sudden death, a danger which may be increased by a general anesthetic or surgical procedure. The risk is greatest in those patients who have experienced dizziness, syncope or angina pectoris. The surgical mortality rate also rises in cases of rheumatic heart disease when the patient passes the age of thirty-five, for developing coronary arteriosclerosis often impairs the blood supply required to maintain compensation by the enlarged heart. Rheumatic cardiac patients are susceptible not only to the more general risks of surgical operations but also to an activation of rheumatic fever and to a complicating bacterial endocarditis. The latter is most apt to follow dental operations and operations on the genitourinary tract.

Hypertension. Operative procedures are tolerated virtually as well by patients with uncomplicated hypertension as those with normal blood pressure. Among other evidence to support this opinion is the minimal operative mortality associated with extensive sympathectomies, even in cases of malignant hypertension. However, the surgical risk in most major operative procedures on hypertensive patients increases when there is evidence of cardiac insufficiency, severe coronary disease, renal impairment or a previous cerebral accident. In the presence of these complications operation is permissible only when the surgical indication is absolute.

Coronary Artery Disease. The surgical risk is higher with coronary artery disease than with other cardiac diseases. Therefore it is especially important that the surgical indication be unequivocal. However, it is important to emphasize that major surgical operations are well tolerated by the great majority of patients with clinical coronary disease. Brumm and Willius[6] reported only 11 cardiac deaths (4.3 per cent) among 257 patients with severe coronary artery disease undergoing major operations. The mean age of these patients was sixty years. There was a history of previous myocardial infarction in 32 and a history of angina pectoris in the remainder. However, the incidence of pure cardiac deaths may not reveal the entire picture since cardiac patients may suffer more "noncardiac" complications, and succumb to these more frequently than patients without heart disease.

Frank heart failure increases the surgical risk in patients with coronary disease as it does in rheumatic patients but the close correlation with degree of functional impairment is absent. The risk of myocardial ischemia and the danger of postoperative myocardial infarction or of sudden death due to ventricular fibrillation or other cause are complicating factors.

Surgical risk is greatly enhanced if operation is performed in the course of a recent myocardial infarction. Unless there is an acute emergency demanding immediate operation, surgical procedures should be delayed at least three months following the acute myocardial infarction. If there is a history of increasing frequency of angina pectoris or of its occurrence with less and less provocation, an impending coronary occlusion is probable and operation should be avoided or delayed if possible. The association of Adams-Stokes syndrome also adds to the risk of operation and the latter should be performed only for urgent emergencies.

Syphilitic Cardiovascular Disease. In asymptomatic cases operation is usually well tolerated. In the presence of angina pectoris or heart failure the surgical risk increases considerably.

The risk associated with other less frequent cardiac conditions has been insufficiently studied. Auricular fibrillation and other arryhthmias do not enhance the risk if the ventricular rate is well controlled and cardiac function is good. Major surgical operations are usually well tolerated despite the presence of bundle branch block.[13a]

THE CHOICE OF ANESTHESIA

The anesthetic agent, administered by a skillful anesthetist, is rarely a significant factor in surgical risk, either in the cardiac or noncardiac patient. However, the diseased heart is usually more sensitive to myocardial anoxia and therefore to deficient oxygen in the anesthetic mixture. This applies particularly in cases of advanced coronary arteriosclerosis, aortic stenosis, syphilitic coronary ostial stenosis, and those with Adams-Stokes syndrome. Sudden and severe reductions in arterial pressure are also particularly dangerous to these patients with diminished coronary reserve. In the above-mentioned groups of cases, there is a tendency to sudden death and factors impairing coronary blood flow or myocardial oxygenation increase that tendency. The pharmacologic effects of anesthesia on the heart have been reviewed by Meek.[12] Electrocardiographic abnormalities have been described in about 80 per cent of a series of 109 patients under anesthesia with various anesthetics in current use.[10] Sinus arrhythmia, premature beats, occasional disturbances in conduction, and transient variations in the amplitude of the QRS complex and T waves were described.

The oft-stated rule that the choice of the skilled anesthetist is more important than the type of anesthetic agent bears repetition. As a corollary it may be said that in operations on cardiac patients the anesthetist should choose the anesthetic with which he has the greatest familiarity and skill rather than a theoretically preferable one with which he has had little experience.

Local anesthesia with procaine or similar preparation should be used when possible for minor operations. Epinephrine is best avoided in all cardiac patients and is contraindicated in patients with coronary artery disease. Barbiturates should be administered before the use of procaine. If local anesthesia appears inadequate or undesirable, sodium pentothal in 2 to 3 per cent solution may be given intravenously for minor operations or for extraperitoneal operations which are not very long and which do not require great abdominal relaxation. Inhalation of 100 per cent oxygen and maintenance of an airway are important adjuncts to pentothal anesthesia. Intravenous pentothal may also be combined with a 50 per cent mixture of nitrous oxide and oxygen.

The most reliable inhalation anesthetic for major operations in cardiac patients is ether because of maximal experience with this agent and because of the absence of serious disadvantages. Ether is administered by means of the carbon dioxide absorption technic. Nitrous oxide with at least 50 per cent oxygen may be used for induction. A combination of cyclopropane with ether and oxygen may give a smoother induction with pleasanter awakening and less nausea or vomiting.[5]

Cyclopropane, without ether, is undesirable because of the risk of inducing serious cardiac arrhythmias especially in patients with coronary artery insuf-

ficiency. It is therefore permissible only for induction of anesthesia and then in combination with high concentrations of oxygen. Nitrous oxide and ethylene are undesirable in cardiac patients because they are not combined with sufficient oxygen when the concentration of these agents is high enough to produce adequate anesthesia. Chloroform should not be used in cardiac patients because of direct toxic effect on the heart. Epinephrine should not be administered during general anesthesia, and especially with cyclopropane, because of the danger of causing ventricular fibrillation and cardiac arrest.

Spinal anesthesia is usually avoided in cardiac patients (except in vaginal or rectal operations) because of the danger of a sharp reduction in diastolic pressure. The contraindication applies particularly to patients with a high diastolic blood pressure. However, this objection may be overcome by the proper use of vasopressor drugs, such as neosynephrine, and the concomitant administration of 100 per cent oxygen. Pituitrin should not be used for its vasopressor effect because of its pronounced coronary constrictor action. In some patients with congestive heart failure inhalation anesthesia may be entirely undesirable and the most satisfactory anesthesia may be obtained with spinal anesthesia in combination with 100 per cent oxygen and a continuous intravenous drip of sodium pentothal.

When arrhythmias or cardiac arrest occurs during anesthesia, epinephrine should not be administered, as is often done. Control of arrhythmias has been reported following the intravenous administration of 30 to 70 mg. of procaine.[7] Cardiac arrest should be treated by massage of the heart directly or through the diaphragm while artificial respiration with 100 per cent oxygen and a clear airway are maintained.[3, 2, 1, 14] In the presence of ventricular fibrillation, defibrillation has been effected by the passage of an electric current through the heart. In operations on the heart itself, ventricular fibrillation may be avoided by maintenance of an adequate supply of oxygen, by the prophylactic infiltration of the heart with procaine[4] and by minimal handling and displacement of the heart from its physiologic position.

MANAGEMENT OF THE SURGICAL CARDIAC PATIENT

In general the same rules of good surgical practice apply to cardiac as to noncardiac patients. Only special points referable to the cardiac patient are briefly considered in the following discussion.

Preoperative Management. The intravenous administration of sodium-containing fluids, including blood, plasma or amino acid infusions, should be avoided, or if essential, must be conducted with special caution as to quantity and rate of infusion. The advisability of giving packed red blood cells instead of whole blood should be considered. The patient's head and shoulders should be elevated during the infusion. Frequent examinations of the chest, determinations of vital capacity, circulation time and venous pressure and questioning as to dyspnea and orthopnea may help to avoid pulmonary edema and right-sided heart failure by early discontinuation of the infusion.

If heart failure is present preoperatively it should be controlled by reasonable bed rest, by digitalization of the patient, by restriction of sodium intake and, if necessary, by the administration of mercurial diuretics. The method and speed of digitalization (Chapter 9) depend on the urgency of the operative procedure. If the patient has been previously digitalized, maintenance doses of digitalis should be continued preoperatively and thereafter. When

heart failure is due in part to loss of blood or to anemia of other origin, it may be most readily controlled by correction of the anemia with cautious transfusions or other appropriate therapy.

Similarly the parenteral administration of thiamine chloride and the correction of a protein deficiency are sometimes essential measures in the preoperative control of heart failure. If possible, therapy of heart failure including intelligent bed rest should be maintained for at least two or three weeks after the heart failure is controlled before the operation is performed. But an operation should not be deferred until heart failure is controlled if the heart failure is due chiefly to a condition which the operation is designed to correct, e.g., a constrictive pericarditis or arteriovenous aneurysm. If an operation is performed for a surgical emergency despite the presence of heart failure, 0.25 mg. of ouabain may be administered intravenously and repeated in a half-hour and again in two to four hours if necessary, provided that the patient has not received digitalis in the preceding two weeks. The effectiveness of preoperative control of heart failure is indicated by the experience of Hamilton[9] who reported 144 cases of overt heart failure on admission, in which a major surgical operation performed after satisfactory preoperative treatment was associated with a mortality of only 5.5 per cent.

In patients with angina pectoris the frequent sublingual administration of nitroglycerin preoperatively and the parenteral administration of 0.24 to 0.48 gm. of aminophylline or of 30 to 60 mg. of papaverine may be beneficial.

Special care must be taken to allay anxiety and reassure the cardiac patient before the operation; sedatives should be employed as necessary. Morphine and atropine or scopolamine may be administered one to two hours before the operation but opiates are preferably avoided in elderly cardiac patients. Quinidine may be given preoperatively to patients subject to auricular tachycardias or to frequent ventricular premature beats.

In patients who are to have an operation on the genitourinary tract, as in patients having dental extraction, 500,000 units of aqueous penicillin and 600,000 units of penicillin-procaine should be given immediately before the procedure, because of the risk of bacterial endocarditis. In operations on the urinary tract the preoperative administration of 0.5 gm. of streptomycin and its continuation every six hours for two or three days also appear desirable. The probable advantages of aureomycin await further clinical trial.

Insulin must be given with extreme caution preoperatively to diabetic patients with coronary artery disease lest a resulting hypoglycemia induce a myocardial infarction. Epinephrine, pituitrin and ergot are drugs to be avoided preoperatively, during or after the operative procedure.

Operative Management. Prolonged narcosis should be avoided and to this end the operation should be limited to the essential minimal procedures. The special vulnerability of the cardiac patient enhances the importance of minimal handling of tissues, skillful technic, proper hemostasis and adherence to all other good surgical principles. Loss of blood due to avoidable surgical trauma or improper hemostasis, because of its deleterious anoxic effect on the diseased heart, is especially inexcusable.

Postoperative Care. Attention is directed again to the need for caution in the intravenous administration of blood, plasma or sodium-containing fluids, as discussed above (p. 1037). If fluids must be given parenterally because of postoperative nausea, 5 per cent glucose in distilled water should be adminis-

tered instead of saline. Postoperative distention may be controlled by the inhalation of 100 per cent oxygen, by gastric aspiration with a Levin tube and by control of any postoperative infection; but pituitrin should not be given.

If heart failure develops, the appropriate measures mentioned under preoperative care should be instituted. The excessive parenteral administration of fluids, excessive blood loss during operation and infection are among the common causes of postoperative heart failure in cardiac patients. The particular danger of infection for cardiac patients demands prompt and adequate administration of antibiotics if there is any doubt as to its presence.

The special frequency of phlebothrombosis and pulmonary embolism among patients with heart disease suggests the importance of using anticoagulants (dicumarol) postoperatively as well as other prophylactic measures. These have been discussed in detail (p. 882).

Cardiac arrhythmias following operation usually subside spontaneously in a few hours or days. They may be controlled, if necessary, by the administration of digitalis, quinidine or both.

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INSURANCE AND MEDICOLEGAL PROBLEMS IN CARDIAC DISEASE

The facts of cardiology are no different, when applied to insurance and medicolegal problems, from those of ordinary clinical practice as described in previous chapters of this book. Unfortunately this is not always apparent in the statements of physicians engaged in forensic medicine or in the decisions of judicial referees or courts. There is great need for reorientation of physicians, lawyers, judges and legislators with respect to the medicolegal aspects of cardiology in order to direct their opinions and judgments into greater harmony with the available body of scientific fact. This applies with particular emphasis to the physician, who should not compromise with, nor distort, established facts in order to abet legal interpretations based on erroneous medical concepts. Neither should his opinions be prejudiced by economic, emotional, sociologic, or political bias.

The following pages include brief mention or discussion of some of the more frequent cardiac problems encountered in insurance and forensic medicine. The cardiac facts which should enable the physician to cope with these problems have already been presented in previous chapters.

CARDIOVASCULAR EXAMINATION AND ACCEPTANCE FOR INSURANCE

The medical examiner for an insurance company is often handicapped in making an evaluation of the cardiac status of an insurance applicant. An accurate or complete history is often unobtainable, and facilities for roentgen ray and electrocardiographic examination and sometimes even for complete physical examination are often unavailable, especially when the applicant is examined at his place of employment. Thus moderate grades of cardiac enlargement are undiscovered. In the absence of electrocardiograms severe coronary disease may be overlooked, for the physical examination may be negative and a history of clinical symptoms may be concealed by the applicant. If there are no facilities for examining the subject in the left lateral recumbent position, an apical presystolic murmur of mitral stenosis may not be discovered.

On the other hand a private physician may tell his patient, after careful examination, that he is entirely normal only to have his application for life insurance rejected because of a cardiovascular abnormality. Or else the applicant is first rejected because of cardiovascular disease but subsequent exam-

ination by his private physician fails to disclose a significant abnormality. In such instances the discrepancy between private and insurance examinations is due to the wide range of normal values and differences in interpretation of borderline findings.

Among the commoner borderline findings responsible for insurance rejection are a systolic murmur, a slightly elevated blood pressure and a rapid pulse rate. The problem of differentiating the insignificant functional from the organic systolic murmur has been discussed (p. 570). The applicant's personal physician, with a complete and reliable history and every needed diagnostic aid, may reasonably conclude that a given systolic murmur is functional and not due to cardiac disease. Without these advantages, of accurate history and complete diagnostic facilities the insurance examiner may be inclined to interpret the murmur as being more significant. Not infrequently individuals with an inconsequential systolic murmur are rejected for life insurance because of the greater than standard risk associated with any large *group* of persons with a systolic murmur. Reversal of this judgment may follow appeal to and more detailed reexamination by physicians at the home office of the company.

The range of normal blood pressure is not sharply defined. If 140 and 90 mm. Hg are chosen as the upper limits of normal systolic and diastolic pressures respectively, many normal individuals may be refused insurance or compelled to pay increased rates. On the other hand more liberal interpretations of normal would result in the insurance of many individuals with a higher average death rate than that of more rigidly normal controls. Even when a definite elevation of blood pressure is found to be transient, the applicant may be considered less than a standard risk from the actuarial viewpoint. For there is evidence that persons with transient hypertension are much more prone to the later occurrence of sustained hypertension and cardiorenal disease than normal controls. A tachycardia, even if transient, may likewise be associated with increased life insurance risk since individuals with transient tachycardia are also found to develop sustained hypertension and cardiorenal disease more often than normal controls.

Other borderline cardiac findings sometimes responsible for increased insurance rates or rejection of individuals whose hearts are probably normal include premature beats, pronounced bradycardia, and T wave abnormalities in the electrocardiogram due to rotation or other positional changes of the heart. It is therefore often helpful and desirable for the applicant's physician and the insurance medical examiner to cooperate in determining as accurately as possible the significance of these minor deviations in the particular individual in question. It is unfair to apply the less favorable prognosis of a heterogeneous group with a given cardiac finding to every individual with that finding when it may be possible to demonstrate its insignificance in a given instance.

WORKMAN'S COMPENSATION AND HEART DISEASE

Most of the medicolegal problems involving cardiac disease arise in connection with claims for workmen's compensation based on cardiac disability or death attributed to an unusual strain or injury suffered unexpectedly in the course of the claimant's employment.

Preexisting Heart Disease. When direct penetrating or nonpenetrating injuries affect the precordial region, cardiac disability may occur whether the

heart was previously well or diseased. On the other hand there is virtually no substantial evidence that strenuous exertion can damage the normal heart. Yet most of the claims for compensation are based on cardiac disability due not to direct trauma but to unusual exertion, lifting or other physical strain. In such cases it follows from the above that a causal relation between the strain and the cardiac disability appears more probable in the presence of preexisting cardiac disease than in its absence.

Since cardiac disability is the usual natural consequence of organic cardiac disease, it would appear illogical, in the presence of preexisting disease, to attribute such disability to some extraneous exertion with any high degree of probability. But according to most compensation laws preexisting cardiac disease is no bar to compensation if the actual disability or death is deemed to arise from some unusual and extraordinary exertion connected with an individual's employment. This exertion or strain is interpreted as the determining cause of disability if it aggravates or accelerates the course of the underlying disease and thereby leads to cardiac disability or a fatal end sooner than would otherwise have occurred. Furthermore most workmen's compensation decisions have failed to apportion responsibility between the underlying cardiac disease and the strain. When cardiac disability was held to result from such strain, the latter was deemed totally responsible.

From the medical, as contrasted with the legal, viewpoint the physician must attempt to assess the probable natural course of the underlying cardiac disease on the basis both of known data concerning the disease and of its history in the individual in question. Then he must estimate whether the underlying disease was unusually and unexpectedly aggravated or accelerated, and if so, whether the alleged strain was the probable cause of this unfavorable acceleration. This decision is particularly difficult because coronary thrombosis, serious arrhythmia and heart failure often appear suddenly and unexpectedly in the natural course of the preexisting disease without unusual exertion or other apparent cause. Certain diseases, such as coronary arteriosclerosis with angina pectoris or coronary occlusion, calcific aortic stenosis and syphilitic aortitis with coronary ostial stenosis, are apt to terminate in sudden, unexpected death independently of any physical strain. There is rarely a scientific medical basis for deciding whether sudden death in the presence of these diseases was precipitated by physical strain arising in the course of employment or was a natural phenomenon of the disease. When an individual suffers from preexistent calcific aortic stenosis or heart block, he may experience attacks of dizziness or syncope which may be fatal. In the course of such an attack he may suffer an injury which is the result of the fatal cardiac episode rather than the cause.

The Relation of Strain to Cardiac Disability. In actual medicolegal practice the physician is queried much less about the pathology, symptomatology or natural course of the preexisting disease than about the role of some physical strain or "accident" in producing angina pectoris, coronary occlusion, myocardial infarction, a disabling arrhythmia, heart failure or unexpected death. Unfortunately the answers to this latter question are rarely strongly buttressed by scientific factual data. They are often determined by personal estimates of probability and reasonableness with emphasis on a post hoc propter hoc type of logic. Frequently the physician is called upon to give his answer in a "yes" or "no" form to an hypothetical question when neither the question nor the

answer fully encompasses a just consideration of all the facts and all the gaps in our medical knowledge.

The physician must first determine the presence and degree of cardiac disability following the alleged injury and whether this differs from any disability present prior to the injury. The most frequent manifestations attributed to cardiac strain include more or less immediate cardiac pain, acute dyspnea, faintness, dizziness, syncope or collapse, cold sweat, palpitation and cardiac irregularity followed by subsequent recurrent angina pectoris or evidence of myocardial infarction or congestive heart failure. Confirmation of a change in the cardiac status may be supplied by serial electrocardiograms following the injury, especially if they can be compared with electrocardiograms taken previous to it.

The physician must then determine whether the given strain was adequate to produce the cardiac disturbance and whether, considering the complete history and findings, the strain in all probability did cause the disability. Various criteria have been proposed as a basis for relating cardiac disability to a physical strain, among which the following may be mentioned: (1) the physical exertion is of unusual severity and more intense or involving greater strain than that previously regularly performed by the affected person; (2) the onset of symptoms of cardiac strain is relatively sudden and follows immediately or very soon after the alleged causative exertion; (3) physical exertions previously executed without difficulty cannot be undertaken or endured. It must be apparent that since preexistent heart disease is usually present satisfaction of these criteria does not exclude the possibility of coincidence rather than causal relationship.

According to most workmen's compensation decisions involving the heart, compensation is awarded for an "accidental injury," sustained in the course of and arising out of an individual's employment, which causes disability of the heart, aggravates or accelerates preexisting disease or causes sudden death. An accident is interpreted as an unforeseen and unexpected occurrence and includes extraordinary physical strain which is not usual to the employment. In addition to lifting, straining and other physical exertions, accidental injuries causing coronary insufficiency or heart failure have been ascribed to "nervous shock," exposure to toxic gases including carbon monoxide and sulfur dioxide, infections sustained in the course of employment, electric shock and even to an injection of tetanus for a wound received in the course of work. The development of heart failure in association with lower nephron nephrosis due to carbon tetrachloride exposure may soon be an additional basis for workmen's compensation claims.

Degree of Disability. Total and Permanent Disability. Having stated that, in his opinion, there is cardiac disability due to some "accidental" extraordinary exertion the physician may be asked to assess the degree of disability sustained, and to state whether this disability is temporary or permanent. From the medical viewpoint it should be emphasized that neither the existence of clinical manifestations of coronary sclerosis including those of myocardial infarction, nor the presence of electrocardiographic abnormalities, nor even the mild grades of cardiac failure, denotes total and permanent disability. A substantial percentage of individuals return to gainful employment following recovery from an acute myocardial infarction. Because of differences in individual response to disease the evaluation of partial or total disability should

be made individually in each case and not on the basis of the general etiologic or pathologic diagnosis. Evaluation of "permanent" disability is often equally difficult because of the well known hazard of prognostication. The word "permanent" must be used with the reservation that it may be subject to revision after continued observation.

Workmen's compensation decisions interpret "permanent" and "total disability" very liberally. It is unnecessary for the claimant to be entirely incapacitated or inert. It suffices to prove that his disability prevents him from performing, in his usual manner, all the essential duties of his occupation which his age, training, experience and physical condition would permit if not for the accidentally induced cardiac infirmity. Thus disability is interpreted in terms of the employe's particular occupation, business or profession and not in terms of other forms of employment or of general physical capacity.

Coronary Artery Disease. Most claims of compensation for cardiac disability allege the production of angina pectoris, coronary thrombosis or myocardial infarction by unusual physical strain or less often by toxic agents, infections or emotional shock. A causal relationship between penetrating or nonpenetrating chest trauma and coronary and myocardial injury is well established by scientific medical evidence (Chapter 44). But the evidence linking physical strain to coronary thrombosis is tenuous.

Our present medical knowledge indicates clearly that coronary thrombosis and myocardial infarction almost always occur on the basis of preexisting, severe coronary arteriosclerosis, whether or not there was manifest clinical evidence. The thrombosis or occlusion is a common inherent incident in the natural life history of the progressive coronary arteriosclerotic process, and in 95 per cent or more of cases it appears without causal relation to any unusual physical strain. It occurs at least as often among sedentary as among manual workers and at rest or sleep as often as during activity.

In occasional instances coronary occlusion is preceded by such an intense and extraordinary physical strain, the previous history is so apparently free from cardiac abnormality, and the onset of cardiac manifestations occurs so promptly after the strain, that it is difficult to avoid the conclusion that the strain actually produced or precipitated the coronary occlusion or myocardial infarction. Since intimal hemorrhage in an arteriosclerotic plaque may lead to occlusion (p. 415), it has been hypothesized that an unusual physical strain may raise the blood pressure and cause an intimal hemorrhage. It has also been suggested that a severe physical strain, by increasing the work of the heart and its need for blood, intensifies a preexisting relative myocardial ischemia to the point of necrosis (infarction).

The difficulty of relating a coronary occlusion and myocardial infarction to a physical strain increases when distinctive clinical manifestations appear only after an interval of many hours, days or weeks. Yet there is evidence that such an interval may actually elapse between the onset and the full development of coronary occlusion and cardiac infarction. Occasionally a transient minor or severe clinical symptom occurring immediately after an unusual exertion appears to be followed by complete recovery. Only days or weeks later is the evidence of recent myocardial infarction discovered, and the claim is made that the initial immediate symptom represented the onset of a coronary occlusion due to physical strain. This type of case stresses the value of

routine and repeated electrocardiograms promptly after any unusual effort which is suspected of having caused cardiac injury.

Sometimes a traumatic injury is followed by infection and prolonged invalidism and culminated by a disabling or fatal coronary occlusion. Even in such cases courts or referees have affirmed a causal relation between the infection and physical and mental suffering and the coronary occlusion, even though much more hypothesis than medical fact is adduced to support such an interpretation. Rarely a myocardial infarct has been attributed to a coronary embolism arising in a venous thrombus at the site of injury of an extremity. In the absence of cardiac septal defects this could not occur, and even in their presence there is no evidence that coronary embolism and cardiac infarction do occur. In this connection the section on fat embolism should also be reviewed (p. 885).

Valvular Disease, Arrhythmias and Heart Failure. Penetrating and nonpenetrating injuries of the chest may cause myocardial contusion, pericarditis or hemopericardium, arrhythmias, rupture of valves or heart wall and heart failure or rapid death. In some instances of nonpenetrating chest trauma it is difficult to prove the actual occurrence of cardiac injury but this difficulty can usually be avoided if careful physical, roentgenologic and electrocardiographic examinations are made promptly and repeatedly after the trauma.

An unusual physical strain may rarely rupture the chordae tendineae or cusps of a diseased valve, but extremely rarely if ever is a normal cusp so ruptured. Since rupture of the chordae may occur spontaneously, the extraordinary nature of the alleged strain must be carefully evaluated before it is credited as the causative factor.

Bacterial Endocarditis. This has been attributed to trauma and infection occurring in the course of employment. A decision as to causal relationship may be aided by bacteriologic study of the blood and, if possible, by comparison of the organism obtained on blood culture with that of the organism responsible for the infection in the traumatized area.

Cardiac Neurosis. Not infrequently the persistence of symptoms, such as precordial pain, dyspnea and fatigability, following a chest trauma or an unusual physical strain are due to a cardiac neurosis and not to organic damage to the heart. In this as in other forms of traumatic neurosis early settlement of litigation is often an effective prophylactic against prolonged invalidism.

LIFE, HEALTH AND ACCIDENT INSURANCE

Total and Permanent Disability. The difficulties of evaluating the presence of total and permanent disability in connection with benefits provided under life, health or accident insurance policies are similar to those connected with workmen's compensation claims and have already been discussed. In recent years life insurance claims of total and permanent disability were particularly frequent when an individual suffered from angina pectoris or coronary thrombosis. The economic depression and unemployment undoubtedly increased the pressure to make such claims. In some instances fraudulent claims were supported by electrocardiographic abnormalities secretly induced by digitalis. Fortunately this problem is becoming outdated as life insurance policies with benefit provisions for total and permanent disability have been granted rarely in recent years

Accidental Death and Double Indemnity. One of the problems arising in association with life insurance policies is the provision for double indemnity or payment of twice the face value of the policy if the insured dies of an accident. A similar problem occurs in connection with accident policies which provide for the payment of a lump sum in instances of accidental death. We are particularly concerned with those instances in which the accident is claimed to have caused a cardiac death. But in contrast with claims of workmen's compensation, it is necessary to prove that death occurred exclusively as a result of an accident, independent of any preexisting disease. Under such circumstances it may be relatively easy to demonstrate a causal relationship between death and penetrating chest wounds, severe nonpenetrating chest trauma, and occasional toxic agents if the onset of symptoms is immediate, and death occurs promptly or as an end result of an uninterrupted progression of the immediate symptoms. On the other hand it seems impossible to justify a cardiac fatality, on the basis of an extraordinary physical strain, if the heart and coronary arteries are presumed to have been previously free from disease. In practice, however, the problem is made difficult by the claim that any preexisting disease was inactive or arrested and that the fatal cardiac disturbance must be attributed entirely to the accidental strain which activated the "arrested" disease. The physician who is required to give an opinion should adhere as far as possible to a presentation of what is known medically without becoming involved in inconsistent legalistic definitions or interpretations. From the medical viewpoint, any opinion as to possible relationship between a given stimulus and a cardiac fatality should be the same whether given before a workmen's compensation referee or in a court trying an insurance claim for accidental death.

PERSONAL LITIGATION

The medical problem in personal litigation (tort law) arising out of cardiac injuries is identical with that described under the above headings. The physician may be asked for an opinion as to the presence of cardiac disease, the degree and duration of disability and whether a given alleged injury in all probability was responsible for the cardiac disturbance. In practice the problem in personal litigation differs from that of workmen's compensation in that liability of the defendant must be demonstrated on the basis of intentional or negligent exposure of the claimant to the injury. Furthermore such compensation as the claimant may be awarded for medical, hospital and nursing expenses, pain and suffering, loss of earnings and other items may depend on what percentage of the disability is due to the accident and not to preexisting disease. The physician may then be confronted with the difficult task of estimating this percentage.

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